# SHOCK AND CIRCULATORY HOMEOSTASIS

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*Transactions of the Fourth Conference*
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*Fourth Conference on Shock and Circulatory Homeostasis*

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*Fourth Conference on Shock and Circulatory Homeostasis*

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# THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

CONTINUOUS ADVANCE in the field of medicine requires not only new discoveries at the frontiers of knowledge but also effective communication among investigators. New "break-throughs" at any one spot may depend upon the integration of insights and technical skills derived from widely disparate areas of scientific investigation.

The growing volume of scientific publications in itself imposes a heavy burden upon the investigator to keep abreast of advances in his own field and discoveries in other branches of science pertinent to his particular interest. But there is another aspect of communication, a more personal one, which has to do with the tendency of scientists at their meetings to accept the lecture or other formal, and hence uninterrupted, presentation as the major means of communication. There are a number of obstructions to communication by this method, some of which are obvious, such as problems of national and technical language. Others, less evident and therefore more difficult to cope with, are psychological and cultural. These have to do with unrecognized blind spots, prejudices, and overattachment to or dependence upon an "authority," or upon too narrowly conceived criteria of credibility. Such hidden obstructions to communication form a major source of misunderstanding and even hostility among scientists and threaten to delay the acceptance or proper evaluation of new data and particularly to prevent genuine cross-discipline understanding and multidiscipline team work.

The Conference Program of the Josiah Macy, Jr. Foundation has gradually evolved in an effort to deal more effectively with these hidden obstructions to communication. The participants are limited to twenty-five—fifteen to twenty regular members who attend the five annual meetings of each group and the remainder guests invited to one or more meetings. The group lives together for 2 days at a small inn, away from the distractions of a large city, where the informality of arrangements contributes to the development of a warm and friendly atmosphere.

The emphasis upon discussion, provided for by limiting the presentations to one, or at the most two, per day and by encouraging interruptions at any time during the presentation, and the tradition, now well established, that "authority" carries little weight in evaluating the credibility of ideas, concepts, and data, help to make the conference a forum for

searching examination of differences of opinion and of the reasons for contradictory experimental results. Overgeneralizations are quickly met with the question "with respect to what?"

In the atmosphere of such a meeting it is often possible to discover the basis for contradictory findings. Thus the "failure to confirm" is frequently found to be due to previously unrecognized differences in experimental procedure. At such a meeting a scientist may discover that his hostility to the concepts or data of another is engendered by the cross-cutting of two contradictory but overgeneralized conclusions. Once the overgeneralizations are "cut down to size," i.e., made to conform to the limits within which there are supporting data, the threat to his position disappears and hostility is often replaced by acceptance or constructive criticism.

Members of the conference group become friends, spontaneous collaboration follows naturally. With the growth of mutual confidence, the members bring unpublished data and plans for experiments to the conference in order to obtain critical judgment and suggestions from the group.

Finally, as an atmosphere of "free-floating security" is established, the group becomes increasingly creative. New suggestions for research and working hypotheses are freely put forward, to be discarded, amended, or subsequently tested by experiment. Often the most constructive suggestion comes from a participant not immediately concerned with the problem under discussion and able, therefore, to see the issue with fresh perspective. A genuine partnership in the growth of ideas is the goal.

The transactions of the conferences are published in order to share the experience of the meetings with a larger audience. Although verbatim reporting is impractical every effort is made to preserve the spirit of the conference. Each participant is given an opportunity to edit his own contributions. The Medical Editor in co-operation with the Foundation staff reserves, however, the liberty to make some rearrangement of material to provide better continuity for the reader.

The Foundation looks upon the Conference Program as an experiment in communication, still in progress.

FRANK FREMONT-SMITH, M.D.
*Medical Director*

# ACTION OF EPINEPHRINE IN MAN

HENRY BARCROFT
*Sherrington School of Physiology*
*St Thomas's Hospital*
*London England*

I would like to describe for you some experiments involving the administration of epinephrine to man Although not all of these experiments were performed in our own laboratory some of them were and I am fairly familiar with those that were not

These experiments show the action of epinephrine not only on the circulatory system but also and in a more marked degree on the nervous system however as the action of epinephrine on man s nervous system is in itself interesting and may have implications as regards the circulation perhaps for that reason there may be some justification for discussing it at this time

The majority of the experiments were performed on voluntary human subjects In general the epinephrine was infused into the antecubital vein while the subject lay on a couch In control periods saline alone was infused and during experimental periods saline plus epinephrine was administered Both were infused from a mechanically driven syringe at a constant rate of 4 ml per min Figure 1 shows the infusion machine

I am not going to be concerned at this time with the action of epinephrine on peripheral circulation but I would like to say a word about the symptoms which the subject feels The rate of epinephrine infusion was 10 μgm. per min which is about the same as a clinical dose of 1 ml of 1/1000 administered in approximately an hour and a half

Most subjects are conscious of the fact that their heart is beating rather strongly and with palpitations although it is not beating very fast Many of them also notice that they are breathing more deeply and more quickly than normally This is the first point that I think would be worthwhile discussing in more detail

### EFFECTS OF EPINEPHRINE ON RESPIRATION

Since we had been taught in the laboratory that the action of epi

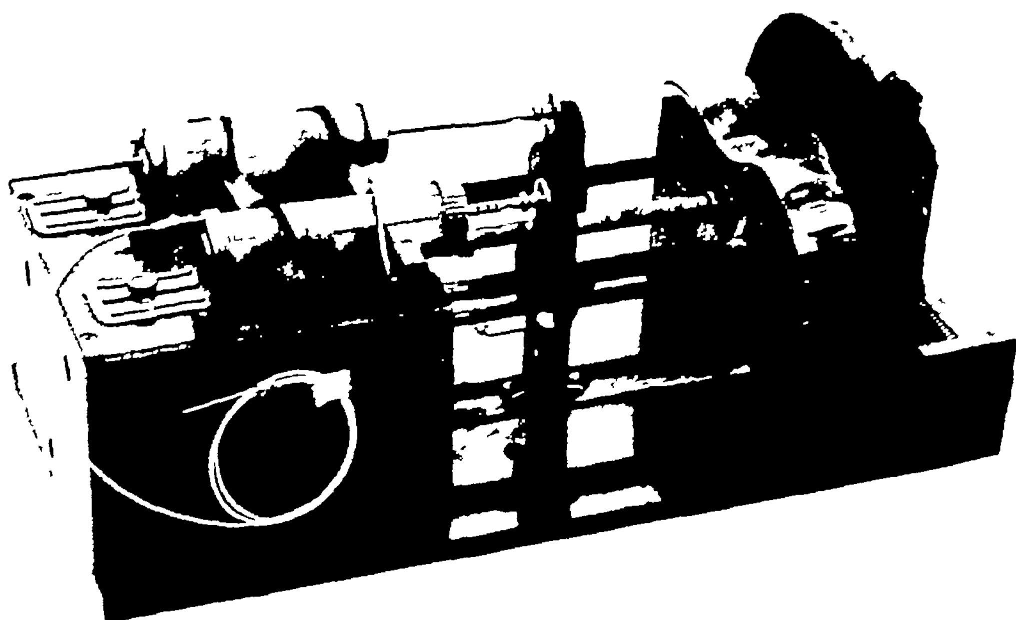


FIGURE 1 An infusion apparatus By alternate use of the syringes, a continuous infusion of saline is given throughout the experiment at the rate of about 4 ml /min As soon as a syringe is nearly empty the adapter on the tubing is pulled off the nozzle and fitted to the nozzle of the syringe The empty syringe is refilled and replaced *Epinephrine is added to the saline as and when required Photo* by P T Machell, Radiotherapy Workshop, St Thomas's Hospital, London Reprinted, by *permission, from* Duff, R S *Effect of sympathectomy on the* response to adrenaline of the blood vessels of the skin in man *J Physiol* 117, *415 (1952)*

nephrine is to inhibit respiration, it did seem rather interesting that when administered to man it should have the opposite effect This question was investigated by two of my colleagues, Dr R F Whelan and Miss Maureen Young (1), who made the infusions with a stethograph in place so that they could record the respiratory changes One of these experiments is shown in Figure 2 * The period of epinephrine infusion is clearly marked and the stethograph record is at the top The conspicuous thing is an increase in the depth of breathing shortly after the administration of the epinephrine The bottom of Figure 2 shows the time in minutes In that particular individual the stimulation lasted for 3 or 4 minutes and then more or less tapered off

*We then began to wonder why it was that epinephrine stimulated* breathing The first thing likely to occur to one is that the epinephrine is stimulating metabolism It is rather interesting to note that in some

*Where adrenaline and nor-adrenaline appear on figures, substitute epinephrine and arterenol

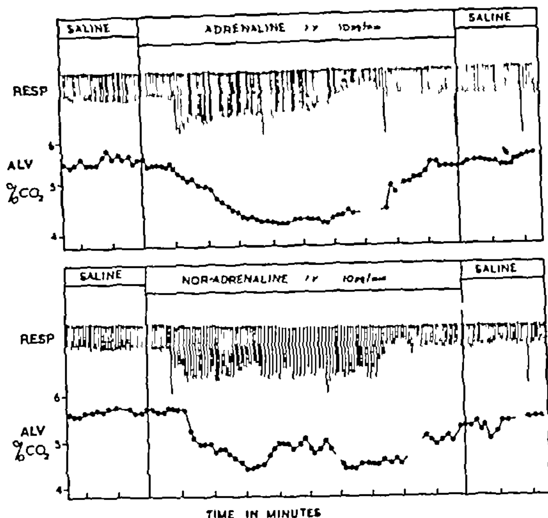



FIGURE 2 Experiment showing that intravenous epinephrine stimulates respiration in some human subjects top tracing—stethographic record of breathing bottom tracing—percentage of $CO_2$ in alveolar air Stimulation of breathing was not due to increase in the $CO_2$ tension of the blood Reprinted by permission from Whelan, R F and Young I M The effect of adrenaline and noradrenaline infusions on respirations in man *Brit J Pharmacol 8 98 (1953)*

individuals arterenol stimulates breathing too and of course arterenol does not have much of a metabolism stimulating effect The graph underneath the epinephrine record in Figure 2 is that of the alveolar $CO_2$ and this shows a definite decrease From this it is evident that the effect on the respiratory center was not due to the fact that epinephrine was *increasing the $CO_2$ tension in the blood* It could be argued that the subject was simply hyperventilating and washing out CO because of psychic disturbance However this was not so one subject promptly went to sleep on the couch *before* he received epinephrine and its infusion while he was asleep caused the typical increase in respiration and decrease in alveolar $CO_2$

Maureen Young, together with Bradley, Gaskell, Holland, and Lee (2), felt that perhaps the effect on the respiratory center might be due to a stimulating action on metabolism which was producing acid metabolites like lactic acid and a change in the pH They undertook to repeat the above observations but this time they investigated the change in pH in the arterial blood rather than the alveolar $CO_2$ concentration Figure 3 shows results which are rather typical of the whole series of experiments In those subjects in which the respiration was stimulated by epinephrine, the pH, instead of becoming more acid, became more alkaline during the stimulation The conclusion drawn from this was that the epinephrine was not stimulating breathing because of the outpouring of any acid substance into the blood stream itself

EFFECTS OF EPINEPHRINE ON THE NERVOUS SYSTEM

During studies with Dr I Starr (3) of the effects of epinephrine and arterenol infusions on the ballistocardiographic records of the heart, I saw a patient suddenly begin to wave an arm in the air I had never seen that happen before We stopped the infusion and the patient returned to the ward, but the recollection of that occurrence remained and the question came to my mind Had the epinephrine had some aggravating action on some latent neurological condition? Later Robert Schwab, who has a great many Parkinson patients, and I tried some epinephrine infusions in Parkinson patients (4) and demonstrated that this substance aggravates the tremors

At a later date a film was made of the results of such experiments by Dr C B B Downman and Dr R S Duff * In these studies the dose of epinephrine was halved to 5 μgm per min In most normal people the effect of 5 μgm per min is minimal, and in many cases the symptoms caused by this dose are not noticeable at all † Figure 4 shows a patient in whom the Parkinsonian tremor was aggravated by epinephrine Loman (5) also has shown that intravenous injections of epinephrine aggravate the tremor

The experiments were repeated using arterenol but the result was different although it raised the blood pressure to about the same extent as the epinephrine Evidently arterenol does not have the same action on the Parkinsonian tremor

These studies seem to indicate that epinephrine has some effect on the nervous system itself There is, however, an alternative explanation—that as a result of the epinephrine the patient is perhaps experienc-

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*Unpublished observations

†At this point in the symposium the above mentioned motion picture film was presented It showed accentuation of the Parkinsonian tremor

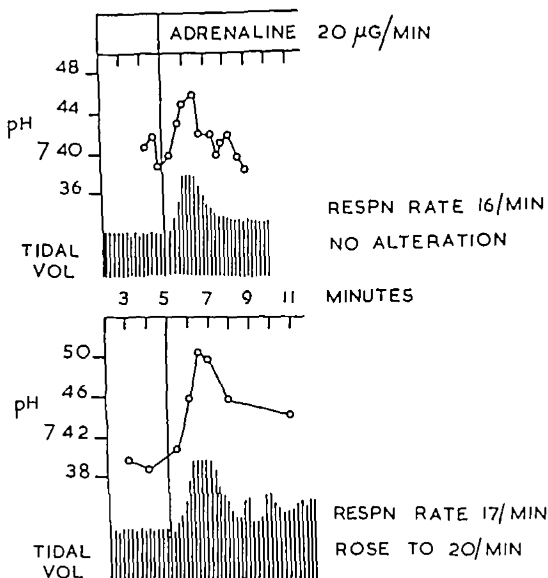



FIGURE 3 Experiment showing that the increase in breathing during intravenous epinephrine infusion in man is not due to lactic or any other acid in the blood During the infusion the arterial blood becomes more alkaline top tracing—arterial blood pH bottom tracing—stethographic record of breathing Reprinted by permission, from Bradley R D Gaskell P Holland W W Lee, G de J and Young I M The acid base changes in arterial blood during adrenaline hyperpnoea in man *J Physiol* 124 213 (1954)

ing some symptoms which in turn induce a feeling of anxiety The anxiety may be the factor which is aggravating the tremor it is difficult to distinguish between the two However if I remember rightly one or two of the patients said that the first thing they were aware of during the epinephrine infusion was the increase in their movements

*Fremont Smith* Is it possible that the last suggestion works just the



FIGURE 4 Photograph made from one of the frames of a film which showed that intravenous infusion of epinephrine aggravated the tremor in three patients suffering from Parkinson's disease The patient seen here exhibited no tremor before the infusion, but the film showed that the intravenous infusion of epinephrine at 5 ml/min soon provoked a marked Parkinsonian tremor Courtesy of Drs C B B Downman and R S Duff in the Sherrington School of Physiology, St Thomas's Hospital, London, England

opposite way, that the epinephrine itself produces, through its effect on the nervous system, a sense of anxiety rather than that the patient is having anxiety in response to some symptoms, and that, therefore, both the breathing and the tremor are the physiological response to endogenous anxiety coming from epinephrine in this case instead of coming from psychological stimulus?

*Barcroft* Yes

*Fremont-Smith* In making rounds it is commonly observed that as the attending physician and his staff are approaching the bed of the Parkinsonian patient, his tremor becomes greater and greater, until, when the group is actually standing before his bed, his tremor has become just as great as that shown in your illustration As the group leaves the patient, his tremor subsides So it would seem to me that since there is other evidence that epinephrine does evoke anxiety by its effect on the nervous system, we may be seeing the effects here of anxiety evoked by epinephrine rather than by the group making ward rounds

*Barcroft* Yes

*Fremont Smith* And this ties together both the effects on the respiration and the effects on the tremor

*Barcroft* Yes

*Bradley* We find that many patients respond to arterenol with feelings of anxiety is that your experience?

*Barcroft* I shouldn t have thought normal subjects would It has not been my experience when moderate doses were administered to Parkinsonian patients either

*Fremont Smith* What doses were you using?

*Bradley* We were giving an infusion of arterenol at a rate of 7 μgm per min In many instances because of discomfort to the patient it was necessary to discontinue the infusion of arterenol although these subjects did not know when the infusion of the drug began since it was administered by injection through a side arm into an infusion system which had been established at the beginning of the study The visceral sensations which some subjects equate with fear others with anger appear only when arterenol or epinephrine is administered

*Stead* Dr E C Kunkle (6) at Duke University has been interested in the problem of how a man feels after the administration of epinephrine he has also been interested in the tremor phenomena He does not believe epinephrine itself is totally accountable for the anxiety but believes that if an individual becomes sufficiently anxious he experiences many sensations like those produced by epinephrine We finally arrive at the point where we must ask what anxiety is and I would not like to go beyond this

*Myers* It might be interesting to mention that in a study of insulin hypoglycemia (7) quite by chance we encountered a patient who had mild if not latent Parkinsonism The hypoglycemia which is known to give increased epinephrine activity precipitated frank Parkinsonian tremor We could not say that anxiety did not have some role in this but the patient did not seem unduly anxious

*Nickerson* Have you studied the respiratory and Parkinsonian effects of sympathomimetics such as amphetamine and desoxyephedrine that are used as central nervous system stimulants?

*Barcroft* No I have not

*Nickerson* It seems to me that the pattern you have described fits in very well with what we might expect from the pharmacology and the structure activity relationship of these compounds Sympathomimetics which have a phenyl ring whether hydroxylated or not have a very significant central excitant effect As far as I am concerned, the only real reason for selecting compounds like amphetamine desoxyephedrine

and ephedrine as clinical central nervous system stimulants is that the absence of the phenolic hydroxyl groups makes their peripheral actions sufficiently weak so that effective doses can be given without markedly altering the blood pressure and heart rate All of the things you have described here would fit into the pattern of stimulation characteristic of a drug such as amphetamine One way of checking this point might be to study the compounds in which the ratio between central and peripheral actions is shifted in the direction of the central effect

I might say one more thing about anxiety Our experience has not been with infusions but with single intravenous injections of 1 μgm per kgm of epinephrine This is equivalent to a small dose for an animal and probably produces higher blood levels than are obtained with an infusion This dose produces marked anxiety even though all phases of the response have been explained to the patient I have experienced this in experiments on myself I knew exactly what was going to happen and yet I could not avoid a sort of latent feeling of terror This reaction is certainly greater than that produced by an equal central stimulant dose of something like ephedrine I think factors other than central nervous system stimulation are involved Palpitation is a significant factor, but it may not account for all of the difference

*Lamport* This response of the patient—feeling subjective anxiety when some of the objective manifestations of anxiety are induced in him—is really, of course, an example of the James-Lange theory of emotions It is interesting that some of the patients respond this way, as you say, and some do not Is it possible that this theory is right for some people and wrong for others?

There is a modern recrudescence of the James-Lange theory in the work of Nina Bull, who has sponsored what she calls The Attitude Theory of Emotion (8) She and her coworkers offer evidence that emotion cannot be experienced subjectively if the body responses and attitudes associated in the individual with this emotion are blocked so that they do not appear I believe there are valid objections to the evidence advanced for Bull's theory, but it may well include a kernel of truth, however, other confirmatory studies are needed *

*Harst* I should like to ask if some of these effects might be the result of ischemia What effect has oxygen lack on the tremor in the Parkinsonian patient?

*Fremont-Smith* Ischemia where?

*Harst* I should think perhaps of the basal ganglia, but reduced oxygen supply to some part of the brain

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*Lamport H Unpublished correspondence with Nina Bull and Blaise Pasquarelli, 1951 and 1953

*Burton* I would rather turn your thoughts to the spinal synapse as being the site of the effect of the epinephrine on the tremor because I think it is involved in a very convenient and plausible theory about the nature of tremor As you know tremor of many types is dependent upon the existence of the afferent arc The theory is that this system of muscle and the afferent arc together are inherently capable of oscillation if released from inhibition or damping by cerebellar and other influences Therefore I would think that most likely the effect of epinephrine is in changing the excitability in the spinal center rather than having some effect in the brain

*M Kinsely* Dr Haist raised the issue of whether some of the changes perhaps were initiated by cutting off oxygen supply to those tissues which were particularly supplied by the arteries which received the epinephrine this can be generalized to all the metabolites as well as the oxygen

Isn t Parkinsonism partly caused by loss of neurons or physical changes in basal ganglia?

*Fremont Smith* It certainly has to do with basal ganglia but I suspect we do not know exactly what

I think there is also no good evidence or at least there is a good deal of negative evidence that epinephrine causes any general vasoconstriction of the blood vessels of the brain This has been worked on for a long time However I do not believe there is any evidence that would exclude the possibility of a localized vasoconstricting property of epinephrine particularly in areas where there is a pathological condition so it seems to me that this question could be answered only by isolating the blood flow in specific areas of the brain I think as far as total blood flow is concerned there is no good evidence of any significant reduction Isn t that correct sir?

*Barcroft* Yes

*Fremont Smith* And this is equally true of the circulation of the sympathetic nervous system

*Haist* It should be possible to investigate this in the Parkinsonian patient by giving him a low-oxygen atmosphere to breathe If there is anything in this theory that procedure should augment the tremor but whether it does or not I do not know

*Barcroft* If I might inject there just a word or two on this very difficult and obscure question, I think Drs King Sokoloff and Wechsler (9) showed quite clearly that infusions of epinephrine do increase slightly the cerebral blood flow Then of course there is the possibility of substances having specific effects on certain parts of the brain I do not know anything about the direct effects of anoxia There is a surgical

and ephedrine as clinical central nervous system stimulants is that the absence of the phenolic hydroxyl groups makes their peripheral actions sufficiently weak so that effective doses can be given without markedly altering the blood pressure and heart rate All of the things you have described here would fit into the pattern of stimulation characteristic of a drug such as amphetamine One way of checking this point might be to study the compounds in which the ratio between central and peripheral actions is shifted in the direction of the central effect

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*Lamport H Unpublished correspondence with Nina Bull and Blaise Pasquarelli, 1951 and 1953

anymore It relieves the tremor but the spasticity still remains In other words and this is true of shivering too if an animal is made to shiver and then the dorsal roots in a limb are cut there will never be any tremor whatsoever in the limb There will be merely stiffness or spasticity Tremor apparently in the peripheral limbs is due to the oscillatory arc which is now undamped although of course it is under the control of higher centers I believe that this is a very reasonable theory

It would be very interesting I think to see whether or not the epinephrine produced anything at all in a deafferented limb I personally would think of this as being a metabolic effect of epinephrine at the site of those spinal centers

*Myers* Dr Shorr reminds me that perhaps in the patient I mentioned the one who had hypoglycemia with the same accentuation of tremor the absolute level of the blood sugar may have had something to do with this That is hard to say because that patient had symptomatic hypoglycemia which I think would be associated with the release of epinephrine Suffice it to say that the administration of glucose intravenously promptly abolished the tremor

*W Kinsely* Were these double blind tests if this term is generally accepted as I mean it? Did the patient know the saline from the epinephrine and did the observer know one from the other?

*Barcroft* The patients did not know After the syringe containing the saline had been changed two or three times the patient was given saline with epinephrine added to it He did not know what the syringe contained The observer did know

*Fremont Smith* You mean the observer might give a clue to the patient?

*W Kinsely* This is one possibility and also it is very difficult to keep ourselves out of an interpretation of behavior

*Barcroft* Yes but I am quite satisfied that epinephrine really does aggravate the tremor

*Fremont Smith* It was interesting to note in your film that the Parkinsonian tremor characteristically disappeared when the patient reached over to pick up a cardboard thus proving that it was a true Parkinsonian tremor

*Burton* I would be very interested to know whether the frequency of the tremor changed however I doubt very much that it did again working on the theory outlined to you It has been shown that the tremor of shivering is governed by the mechanical weight of the limbs as well as the characteristics of the reflex motor arc so that if a limb is loaded the tremor rate is altered This is true of this sort of tremor also

treatment of Parkinsonism which is being worked out on the basis of ligature of the anterior choroid artery which would make the basal ganglia ischemic In the cases that it improves it would seem to be on a basis of anoxia, but perhaps a chronic anoxia of that sort is different from an acute anoxia One is perhaps inclined to think this would not be due to an acute anoxia of the basal ganglia because one would expect that arterenol would have a more definitely constrictor effect than epinephrine on most of the blood vessels of the brain, arterenol should, therefore, cause more accentuation of the tremor than epinephrine does, but in fact arterenol does not accentuate these tremors whereas epinephrine does There is some specific thing about the action of epinephrine—perhaps not vascular—which seems to have this effect

*Fremont-Smith* There is, is there not, a tremor in the normal individual when he is overreacting to epinephrine? The old Gurst test with epinephrine is familiar to us, so that Parkinsonism could be thought of as an accentuation of this It would be interesting to do the same experiment with other forms of involuntary movement and tremor, the tremor of multiple sclerosis, the senile tremor, and other such movements, to see whether one was dealing with a general phenomenon or one which was specific for Parkinsonism It seems to me it opens up a fascinating approach to the whole problem of involuntary movement, about which we know exceedingly little To me, one of the interesting aspects has always been the fact that, as far as I know, all such involuntary movements cease with sleep, I do not know of any of them which continue with sleep It would be interesting to see whether such an injection, given to a Parkinsonian patient while he was asleep, could bring out the tremor or whether it would awaken him at once

*Bing* What about the metabolic changes that can occur in the brain following the injection or infusion of epinephrine? Is there anything known about that aside from the work of Dr Kety? Isn't it possible that some of these phenomena which you observe are actually accompanied by, or due to, changes in cerebral metabolism? Has that been investigated?

*Barcroft* Not as far as I am aware Dr Burton has mentioned a possibility of the accentuation of some spinal reflex The only point I could add to that is that epinephrine itself, when given into the artery of the Parkinsonian patient in such a way that its concentration is increased in the terminal elements alone, is not responsible for this reaction It is definitely not a peripheral effect but an effect on the brain or spinal cord

*Burton* A method formerly used to relieve some patients from Parkinsonism was to cut the afferent nerve but I do not think that is done

*Hunt* Mice with insulin hypoglycemia certainly may become very irritable agitated and jittery before they actually convulse

*Fremont-Smith* Dr Bradley spoke of some patients who became anxious and others who became antagonistic when given epinephrine This is very interesting because it is a fairly general rule that when anxiety cannot be expressed it is very likely to show itself as hostility I was quite struck by this because epinephrine is a drug which rather characteristically produces anxiety and some of the patients did not complain of anxiety but did become hostile

This is very interesting in its own right and it is important also in terms of communication It certainly is true that all of us have had people hostile to our ideas and surely a few of us have been quite hostile to someone else s ideas Perhaps when we find ourselves being hostile to someone else s idea it is because that idea makes us a little anxious it threatens our own point of view and of course we would not admit for a minute that anyone could make us anxious so we repress our tendency to feel anxious and the result is that we feel hostile instead

Perhaps this is something that we can learn about communication in terms of ourselves If we become hostile to anyone else s idea we should ask ourselves why that should make us anxious and likewise if another person becomes hostile to our point of view instead of being angry with him we might say to ourselves that this makes him a little anxious so perhaps we have a clue This does two things It makes one a little more objective to the situation at once and it may give one a better interpretation of how the other fellow is reacting I suspect that anxiety turning into hostility is one of the greatest sources of obstruction to communication in general and to science in particular

EFFECTS OF EPINEPHRINE ON THE BLOOD FLOW IN THE HAND

*Barcroft* Dr H J C Swan (10) recorded blood flow in the hand measured by the plethysmograph (Figure 5) I am not asking you to be concerned with the plethysmographic method but only to limit our discussion to this question of epinephrine the nervous system and circulation For the period shown there was given an intravenous infusion of epinephrine as I have described During the period of infusion, there was constriction in the hand but afterward there was vasodilation A few minutes after the infusion is stopped a flush appears which coincides fairly closely in time with this demonstrable increase in hand flow The arrow shows when the flush began This can be seen fairly regularly in these nine records although the basal level of the hand flow is rather different I am inclined to think that this phenomenon was a sort of reactive hyperemia the blood flow being

so I doubt very much if the rate changed. But did you check that at all? It is quite difficult, perhaps, to do. You would have to have a recording, wouldn't you?

*Barcroft:* I think perhaps we may have done it. If we did, it did not change.

*Fremont-Smith:* I believe Stanley Cobb showed a film years ago illustrating that each of these tremors has its characteristic electromyelogram; it would be very easy to make a myelogram of this and determine whether or not the rate was changing. However, I think that one would probably find, as you indicate, Dr. Burton, that the characteristic pattern remains; it is simply the amplitude that is accentuated.

*Stead:* I think it is worth mentioning that Dr. Barcroft has already shown us what we need to do next, or rather, what he needs to do next, namely, to repeat in the tremor studies exactly what he did with the respiratory studies. He could tell us the difference in the response from internal carotid and vertebral injections, and he might try a catheter in the vertebral artery too.

*Green:* Epinephrine and arterenol in the dog, at least, are fairly potent cerebral vasoconstrictors, whereas, isopropylarterenol is a dilator. It would be interesting to use isopropylarterenol; then one would be able to see whether the effect is a metabolic one rather than a vasoconstricting one in the brain.

*Barcroft:* I would like to return to one point that Dr. Burton raised and unfortunately dropped; that is, aside from the question of the anatomical localization here, I believe he initially referred to the possibility that this was an action on an inhibitory system. It might be an inhibitory system in the brain stem. Although the picture we see is one of excitation, it may be that we are here concerned with the inhibition of an inhibitory system.

*Fremont-Smith:* Of course, it is conceivable that the tying-off of the anterior choroidal artery leads not to just an area of reduced blood supply but to actual necrosis of areas and destruction of certain ganglion cells. Do we know about that, Dr. Barcroft?

*Barcroft:* I am afraid I do not.

*Fremont-Smith:* The cells would be acutely put out of function if the main blood supply to them were to be cut off, so that they would be, to all effect, dead within a very few seconds from the time the artery was shut off; therefore, the permanent effect on the tremor might be caused by their being permanently put out of commission or killed.

*Harst:* Dr. Myers, is it possible to induce a tremor with insulin?

*Myers:* We have no such studies.

*Fremont-Smith* Does the phase of vasoconstriction correspond by chance to the period of hyperventilation? If so don't we know that hyperventilation itself causes vasoconstriction?

*Barcroft* Yes that is perfectly true Dr Fremont-Smith but I do not think this is due mainly to that because as I shall show later this effect occurs if the epinephrine is given intra-arterially into the arm and reaches the hand in such doses as would have very small or negligible effects when the drug traveled round and got into the circulation in general

*Fremont-Smith* But you could obtain an accentuation of two effects where it is given intravenously

*Barcroft* Yes that is perfectly true

*Hast* Would the respiratory effect be in just one phase of respiration? For example with inspiration would there be vasoconstriction? With hyperventilation vasoconstriction occurs in skin but it may not be so for muscle

*Fremont-Smith* But isn't this skin?

*Barcroft* This is the entire hand and from the vascular point of view I think it can be considered to be mainly skin

From Figure 6 another of Dr Swan's blood pressure records it is evident that the increase in flow afterward certainly is not due to any increase in blood pressure in particular the peak of the flow is not at the highest point in the blood pressure That leaves this possibility still open—that it is a kind of reactive hyperemia

Figure 7 shows the same plethysmographic records but in this case infusions of epinephrine were made directly into the brachial artery and doses were appropriately reduced to about one fortieth of their previous value so that the hand received about as much epinephrine as it would have had the epinephrine been given intravenously The calculation is only a rough one and I do not claim that the correspondence is altogether accurate We attempted to ensure that the hand got about the same amount of epinephrine in either class of experiment In these experiments the striking thing however is the absence of overshoot after the epinephrine infusion is finished That seems to dispose of the idea that this is a reactive hyperemia effect This set Dr Swan to wondering then what had caused this effect if it was not a local one Was it because the intravenous epinephrine had liberated some vasodilator substance into the blood stream which was causing this vasodilator effect in the hand?

In order to test that Dr Swan carried out a further set of experiments on subjects who were sympathectomized If intravenous epinephrine liberated a vasodilator substance into the general circulation then the

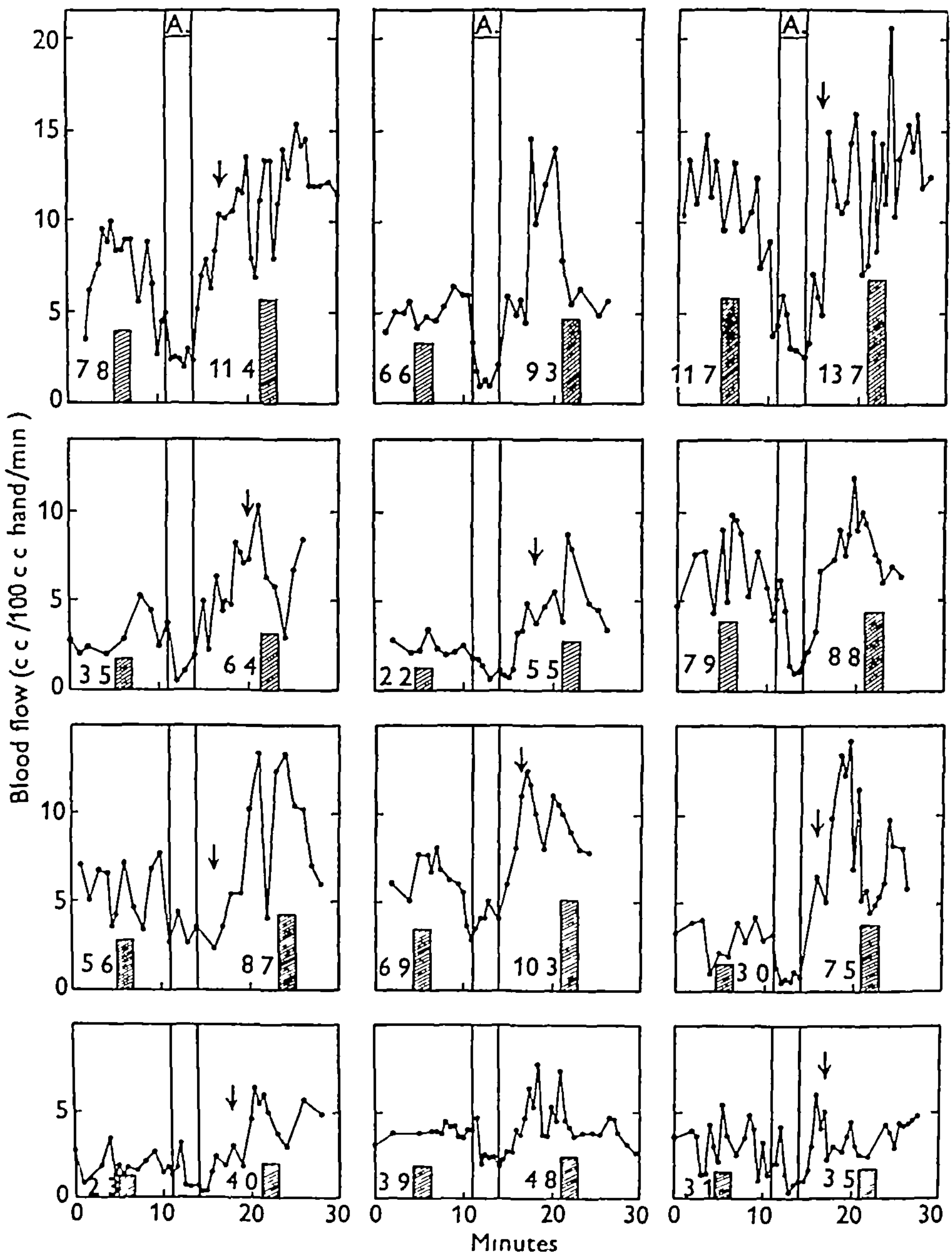



FIGURE 5 Results of twelve experiments showing that intravenous infusion of epinephrine was followed by vasodilation in the hand In each experiment 20 μgm was given for 3 min The infusions were made between the 11th and 14th minutes The shaded blocks represent (half-scale) the average flows recorded in the periods 0 to 10 min and 17 to 27 min The arrow represents the commencement of flushing of the face Reprinted, by permission, from Swan, H J C Observations on a central dilator action of adrenaline in man *J Physiol* 112, *426 (1951)*

shut down by the epinephrine, and that when the epinephrine wore off the local accumulation of metabolites was responsible for this effect

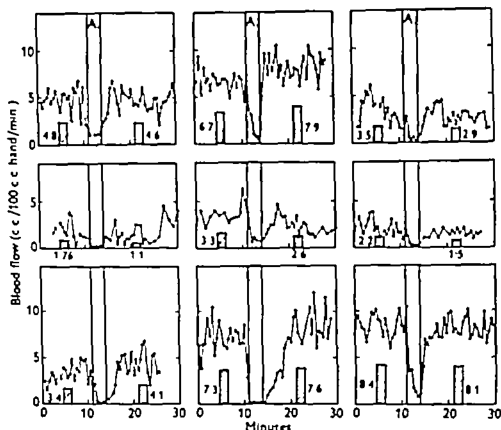



FIGURE 7 Results of nine experiments showing that infusions of epinephrine into the brachial artery are not followed by vasodilation in the hand. ½μgm. epinephrine was given into the brachial artery for 3 min. from the 11th to the 18th minute. The shaded blocks represent (half scale) the average flows in the periods 0 to 10 min. and 17 to 27 min. Reprinted by permission from Swan, H. J. C.: Observations on a central dilator action of adrenaline in man. *J. Physiol.* 112: *426 (1951).*

*Lamport:* Are the epinephrine effects greater with sympathectomized limbs?

*Barcroft:* The constrictor effect of epinephrine is greater in some sympathectomized limbs but not in others.

*Fremont-Smith:* This is a possible interpretation. We do know that if an individual places one hand in hot water, the other hand promptly dilates as if to get rid of the extra heat which is being absorbed in one hand, and vice versa in cold. If one were to assume that the epinephrine administered intravenously in the normal individual caused a fairly general temporary vasoconstriction in the skin, it would reduce the loss of heat over the whole body for a short time and, therefore, there could be a compensatory vasodilation afterward to maintain the homeostasis of temperature control. Your sympathectomized patients apparently

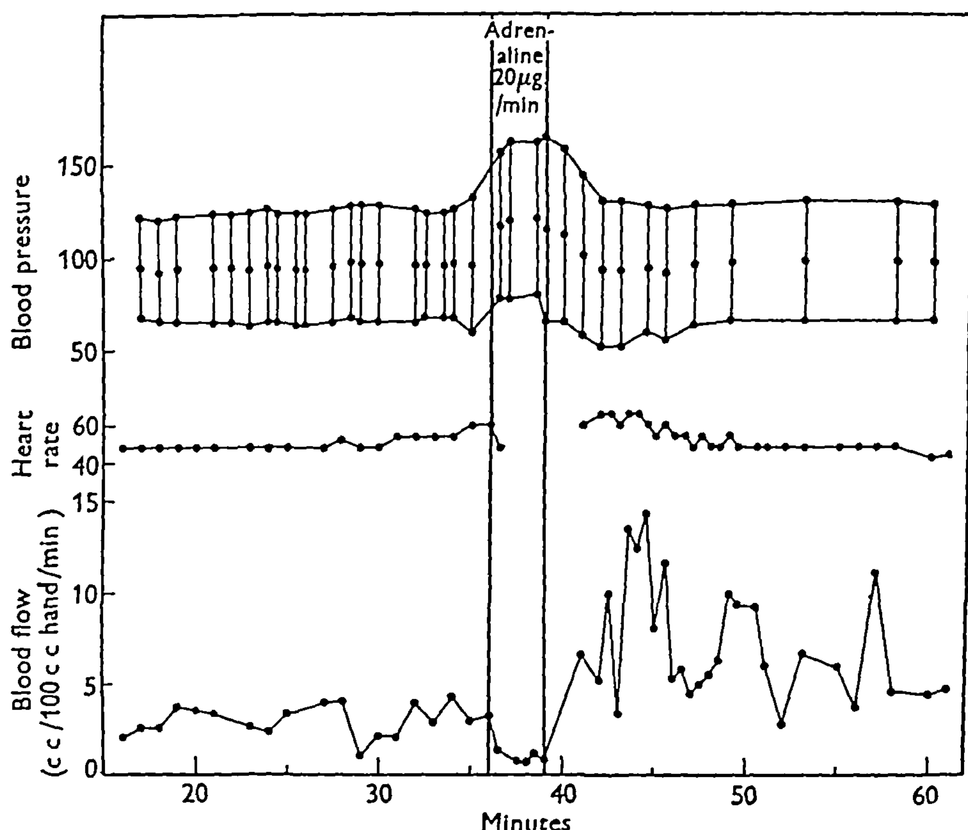



FIGURE 6 Results of an experiment showing that the "after-dilation" in the vessels of the hand following an intravenous infusion of epinephrine cannot be due to a rise in blood pressure The experiment shows that the blood pressure was not raised at the time of the vasodilation Reprinted, by permission, from Swan, H J C Observations on a central dilator action of adrenaline in man *J Physiol* 112, *426 (1951)*

after-dilation" should occur in these sympathectomized subjects Figure 8 shows, however, that the overshoot was absent in the sympathectomized subjects Since the overshoot is absent, the conclusion seems to be, therefore, that the overshoot is present only when the nerves are there and that it is caused by a change in vasomotor nerve tone

Dr Swan therefore thought that the explanation of the overshoot was taking us back again to the action of the epinephrine on the central nervous system, and the situation was that the epinephrine was causing a local constriction of the skin of the hand while it was being infused but at the same time it was having a central inhibitory effect on the vasomotor center However, its effect on the center was marked during the infusion period by a local constriction After the end of the epinephrine infusion, the local effect wore off before the central inhibitory effect and therefore there was a period of dilation Finally the effect of the epinephrine on the center wore off and the blood flow returned to normal

action of the epinephrine on it but because of some action from a higher center such as the hypothalamus in response to the needs of temperature regulation

*Lamport* It seemed to me the amount of epinephrine needed to obtain an effect might be so small because of sensitization resulting from denervation that the central effect of the epinephrine might have been lost even though you were still obtaining the same peripheral effect quantitatively as is found in the nonsympathectomized person I do not know whether that is what you had in mind Dr Fremont Smith but it seems to me relevant In other words was the dose of epinephrine needed much less because the tissues were sympathectomized and therefore sensitized?

*Barcroft* The doses used in the normal subjects were often the same as those used in the sympathectomized subjects

*Fremont Smith* Was this done immediately after the sympathectomy or had there been time for degeneration?

*Barcroft* There had been time for degeneration

*Fremont Smith* Perhaps I misunderstood but I would have expected an exaggerated response in the desensitized person with actual spasms of much longer duration than you obtained in the normal patient

*Barcroft* When the hand is measured in this way as it has been in the further series of experiments by Duff (11) with sensitivity changes after sympathectomy we find that the sensitivity is increased in about six out of ten people after sympathectomy but in the other four there is no change in sensitivity to epinephrine

*Fremont Smith* And these fell in the other four?

*Barcroft* I could not say

*Fremont Smith* That is very interesting

*Green* I wonder if the interpretation of desensitization after sympathectomy has not been overemphasized In a similar study (12 13) we made a series of intra arterial injections in animals before and about 4 weeks after chronic denervation We could find no increase in sensitivity either to epinephrine or arterenol and in view of what Dr Barcroft says I wonder if we are not overemphasizing the importance of this so-called sensitization produced by denervation

*Barcroft* Figure 9 shows some of Dr Duff s sensitivity results It looks very complicated but it is not really At the top are the records of the blood flow in each of the two hands of a Raynaud patient the top two records are preoperative There is a needle in the patient s brachial artery on one side The record from that side is the one with the thick line The other side the broken line was recorded purely for

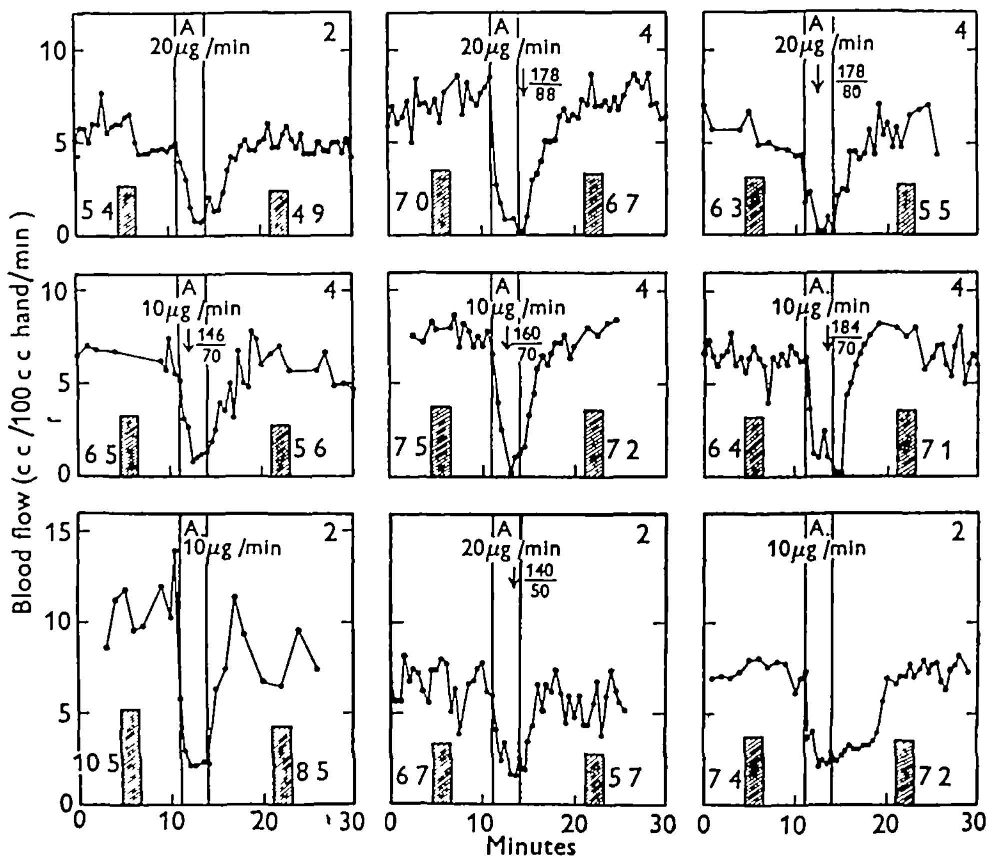



FIGURE 8 Results of nine experiments showing that intravenous infusions of epinephrine in sympathectomized subjects are not followed by vasodilation The "after-dilation" following similar infusions in normal subjects are therefore probably mediated by the vasomotor center and sympathetic nervous system (See previous figure for significance of shaded rectangles ) Reprinted, by permission, from Swan, H J C Observations on a central dilator action of adrenaline in man *J Physiol* 112, *426 (1951)*

reacted to the epinephrine with a vasoconstriction in just about the same manner as the normal patient does

*Barcroft* Yes That was the direct effect of the epinephrine on the blood vessels in the hand They had just the average constriction

*Fremont-Smith* Just as if they had not been sympathectomized

*Barcroft* I think the constriction is mainly due, in normal and in sympathectomized subjects to the direct effect of the epinephrine But I do very much appreciate your point, Dr Fremont-Smith, that it is the normal subjects who have this overshoot Could that be because they were warming up when the epinephrine was being infused?

The explanation that seems to be a very reasonable one is that the vasomotor center is inhibiting its tone not so much because of the direct

is not much effect We then follow that by 1 16 of a μgm and that is followed by 1/8 of a μgm and there is a slight suggestion of constriction with both of those

You will note that in this patient postoperatively there was a greater effect of the epinephrine on the sympathectomized side than on the opposite side which was receiving no epinephrine In this patient therefore sympathectomy had caused some sensitization of the vessels but Dr Duff has tried this with a very large number of these patients and his experience is that about six out of ten hands showed the picture that is given here of increased sensitization and the other four do not show any such sensitization

Furthermore this is not related to the type of sympathectomy on the whole, the ones that do show the sensitization tend to be the preganglion sections the ganglionectomies on the whole tend not to be sensitized So that I would agree Dr Green with what you have said I think that epinephrine sensitization of itself does not explain the absence of overshoot that occurs in the blood vessels following sympathectomy

*Fremont Smith* A very important observation

*Montgomery* Did you do reactive hyperemia tests in the patients with sympathectomized arms and obtain large overshoots?

*Barcroft* I think that Grant (11) showed that reactive hyperemia does occur after sympathectomy

*Montgomery* I thought it might occur in considerably less degree because the initial flow seemed to me to be higher in the sympathectomized hands in your examples so that the top flow might be limited

*Barcroft* On the other side? I do not think they were anything like maximal Dr Montgomery I am sure they were not and I am sure they were capable of dilation

*Burton* Those patients are not in spasm so that the level of blood flow does not mean anything

*Barcroft* Not very much It is interesting that the level is sometimes actually lower 22 days after sympathectomy than it was on the day the patients were examined before sympathectomy

*Fremont Smith* One might hazard that the patient was in a warm room

*Barcroft* Yes both times

*Stead* You might hazard also that the increased sensitivity in the bottom tracing was due to the fact that the sympathectomized hand was more greatly dilated and if you put a little more hot water around the normal hand his responses might have looked much the same

*Barcroft* The dilation is much the same In the after sympathecto-

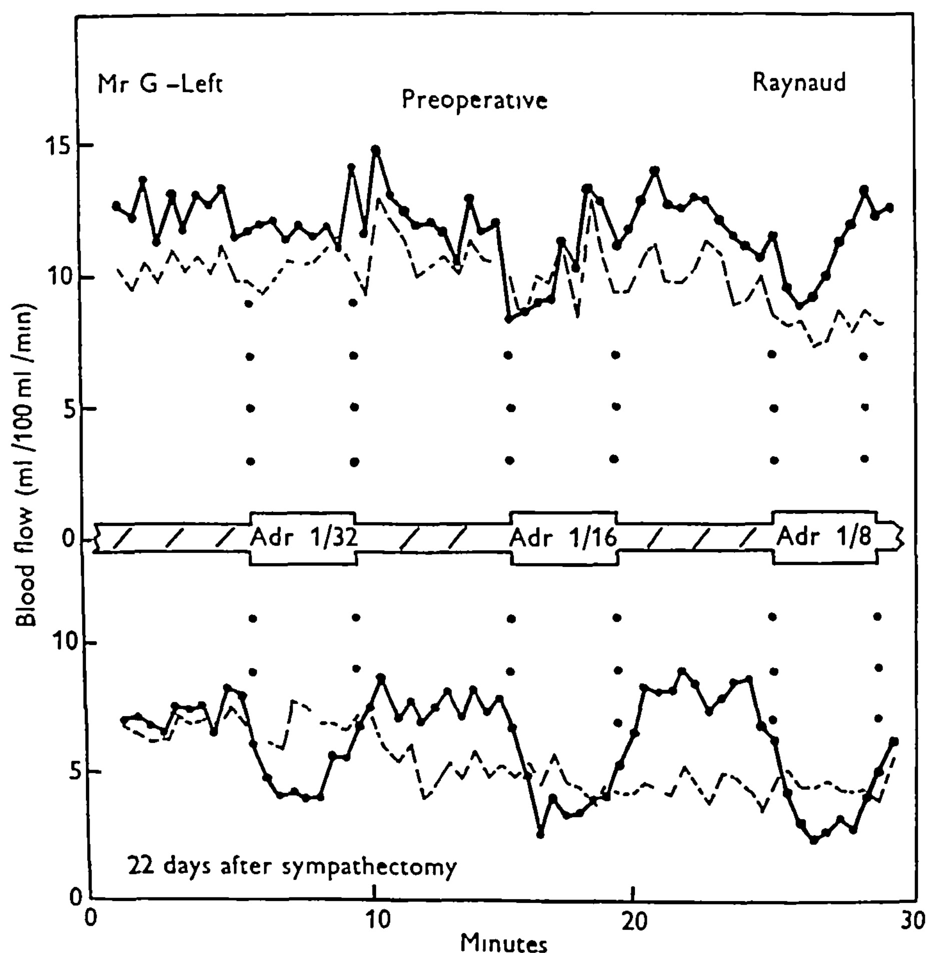



FIGURE 9 Results showing supersensitivity of the vessels of the hand to epinephrine following sympathectomy Blood flow in the left (continuous line) and right (broken line) hands before (top) and after (bottom) operation Saline was infused into the *left brachial artery* throughout each experiment and epinephrine added for short intervals of time in the doses shown on the figure Little or no epinephrine could have reached the *right* hand The vasoconstrictor action of epinephrine on the vessels of the *left* hand was more conspicuous after sympathectomy The fact that these vasoconstrictions did not occur in the *right* hand showed that in the *left* hand they must have been due to epinephrine Reprinted, by permission, from Duff, R S Effect of sympathectomy on the response to adrenaline of the blood vessels of the skin in man *J Physiol* 117, *415 (1952)*

control purposes, so that if diminution in flow occurred it would have significance if there was no similar diminution on the opposite control side

In the middle of the diagram you will see an indication of when the saline was given into the brachial artery, when epinephrine was added to the saline and what the dose of epinephrine was You will see that we start with 1/32 of a μgm of epinephrine and preoperatively there

is not much effect We then follow that by 1/16 of a μgm and that is followed by 1/8 of a μgm and there is a slight suggestion of constriction with both of those

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*Barcroft* The dilation is much the same In the after sympathecto-

mized ones, the initial blood flows, about 7 ml , start off approximately the same in both hands Perhaps I have not understood your point

*Stead* As you follow the tracing along, though, there is much more vasoactivity

*Barcroft* That is so

*Stead* There is never but one base line that is comparable

*Barcroft* In Figure 10, the flow on the control side is only slightly lower

*Stead* This seems more convincing, though

*Barcroft* Yes, I think it is a true phenomenon, all right, on that side You see, we are dealing here with this situation The control hand is used simply to see whether there is a bilateral effect occurring The epinephrine is going solely to the hand which is indicated by the heavy line because it is going into the artery, therefore the difference in the level of flow is not really relevant to this, because the other hand is used simply to indicate whether there are simultaneous changes or not

*Fremont-Smith* Simultaneous directional changes?

*Barcroft* Directional changes, exactly

*Fremont-Smith* But it is not being exposed to the same epinephrine at all

*Barcroft* No

*Burton* We have discussed so many things since you were outlining your prime theories about overshoot, or limitation, could you outline for me what you now think is a tenable theory of this overshoot?

*Barcroft* I would suggest, with Dr Swan, that epinephrine has an inhibitory action on the vasomotor center or on some mechanism that controls the vasomotor center, that when epinephrine is given intravenously it gets into the general circulation and in the hand its action is directly on the blood vessels, causing constriction

There is simultaneously a direct or indirect action on the vasomotor center which causes an inhibition of the sympathetic vasoconstrictor tone but that is not manifested at the time because of the local action of the epinephrine on the blood vessels of the hand When, however, the infusion of epinephrine stops, the local constrictor effect of the epinephrine wears off first, before its inhibitory effect on the center wears off

*Burton* Yes, that is very clear now

*Wood* I should like to suggest that the inhibitory effect may be a reflex one that it seems to me the obvious conclusive experiment is to repeat the intracarotid injections and measure the blood flow of the hand

*Barcroft* Yes If anyone sees the possibility of doing these intra-

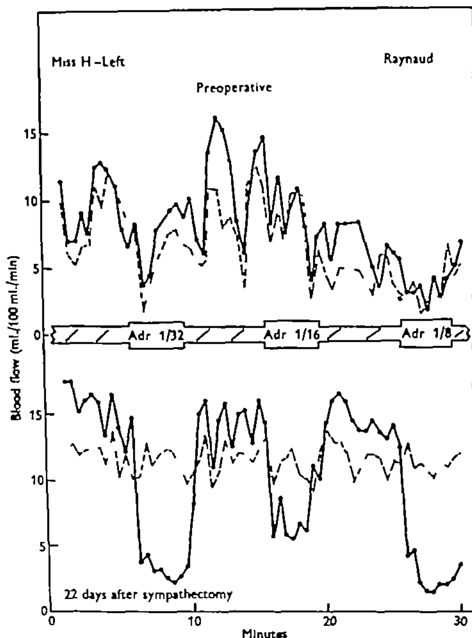



FIGURE 10 Results showing supersensitivity of the vessels of the hand to epinephrine following sympathectomy (For explanation see legend of previous figure) Reprinted by permission, from Duff R S Effect of sympathectomy on the response to adrenaline of the blood vessels of the skin in man *J Physiol* 117 415 (1952)

carotid artery experiments I would be very interested

*Selkurt* It would be a little surprising if you had a central dilating effect that it would not show up with a change in flow on the other side

*Barcroft* No

*Selkurt* Presumably the dose is so reduced that not enough of it gets back to manifest an effect?

*Barcroft* That is right The intravenous ones which we have been discussing were at 10 μgm per min , and here, intra-arterially, we have 0 1 μgm which is 1/40 of that given intravenously, most of this 0 1 μgm will leave the circulation in the capillaries, so I think that explains the difference

## METHODOLOGY

### A PLETHYSMOGRAPHY

I would now like to discuss with you a narrower and much more exact topic—methodology My own experience is limited to work with the plethysmograph, so I thought I might ask you to help me to explain why it is that different methods give different results when applied to the measurement of the effects of intravenous infusions of epinephrine on the blood flow in the forearm My emphasis, though, will be very much on the methods and why they disagree rather than on an explanation of the effect of the epinephrine on the forearm circulation The methods I will discuss are the plethysmographic method, the Hensel thermoelectric needle, the radio-sodium method, and a modification of Krogh-Landis-Turner's capillary filtration method The disagreement between the plethysmographic and the radio-sodium methods has been shown by Dornhorst (15) We shall take these methods into consideration, then in that order

The principles of the plethysmographic method are quite generally known (16) but perhaps we might review them quickly Figure 11 shows the method for measuring the rate of the circulation in the calf, which has been enclosed in a watertight container When it is desired to measure the flow, the cuff around the ankle is inflated to 200 mm Hg to stop the circulation in the foot and approximately a minute later the cuff on the thigh is inflated to approximately diastolic pressure The arterial inflow continues, blood collects in the veins, water is displaced upward in the vertical tube, and air is displaced into the float recorder which draws an upward sloping line on the moving paper

The volume of the calf is measured after the experiment and the float recorder is calibrated the rate of the arterial inflow is calculated from the slope of the curve and expressed in milliliters of blood per 100 milliliters of the calf per minute

*Burton* Dr Barcroft do you think that if the thigh cuff is quite a distance from the beginning of the plethysmograph this can cause an error? I realize in most circumstances it may be necessary to have a space between, but would it not be better to have the cuff closer to the plethysmograph?

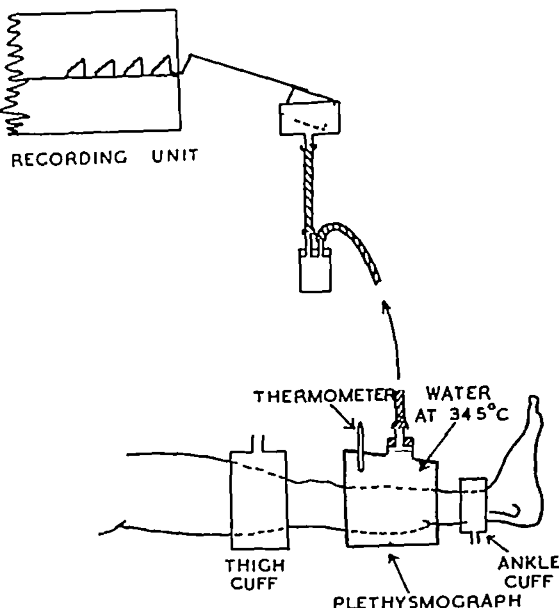



FIGURE 11 Diagram showing the principle of the method of plethysmography as applied to the calf of the leg The ankle cuff is inflated to 200 mm Hg One minute later the thigh cuff is inflated to a suitable pressure somewhat higher than diastolic pressure. Arterial inflow continues for a time unhindered the empty calf veins distend and air is displaced into the recorder which draws an upward sloping line on the moving paper After the experiment, the recorder is calibrated the speed of the drum measured and the volume of the calf found by water displacement. Calf blood flows are then calculated from the slopes of the tracings and expressed in ml /100 ml calf/min Reprinted by permission, from Shepherd, J T *Some Observations on the Collateral Circulation in Man* M Chir Thesis Belfast, Queen's University 1948 (p 55)

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*Barcroft* That is perfectly right

*Lamport* Of course even the upper part of the limb and the lower part would have significantly different effective tissue pressures compared with the exposed limb

*M Kinsely* May I say one thing sir? Oftentimes the utilization or the design of an instrument depends very much upon the purposes for which it is designed The discussion has revolved around the internal construction of the apparatus This certainly should be very useful for some purposes and it may have limited usefulness in others What are the major purposes?

*Barcroft* The purpose of this water plethysmograph is to control the temperature of the limb very carefully so that if the effect of the procedure is being examined the level of the flow before the procedure can be compared with the level of the flow during the procedure There may be quite a long interval between the records perhaps half an hour If during that time the temperature were to change then errors might be introduced, and that is why it is a good thing to have the plethysmograph water filled and at a constant temperature

*M Kinsely* Is the water static or do you circulate constant volumes through the plethysmograph?

*Barcroft* The water is not circulated but ideally it should be stirred all the time and the temperature maintained within the limit of 34 to 35 C It is essentially a constant temperature plethysmograph

*Montgomery* Is one of your purposes in using water of a given temperature to try to keep the cutaneous flow as constant as possible while you are measuring the muscle flow?

*Barcroft* Yes

*Green* Do you think the effect of the temperature in the plethysmograph is due to the effect of the temperature on the organs inside or a reflex effect mediated through the body? The reason I ask is we have been very much unimpressed by the effect of organ temperatures on inherent blood flow if the organ is decentralized

*Barcroft* I had imagined Dr Green, that we were dealing mainly with local effects there Certainly in the chronically sympathectomized limb where the part is separated from the vasomotor center temperature has quite a marked effect on the tissue blood flow (20) *

*Stead* I wonder if it may not reflect the way in which the temperature is changed When the air temperature around a sympathectomized part is changed, I have the impression that blood flow does not change much If a sympathectomized part is put in a water plethysmograph, the blood

*Here again the comment and reference are to cutaneous flow in the hand plethysmograph

*Barcroft* That is right and quite often we do place it just below the knee

*Montgomery* Dr Barcroft, I assume this is a water-filled plethysmograph You have found an optimum temperature for the water

*Barcroft* The plethysmograph I have illustrated here is a water-filled one

*Montgomery* Isn't the temperature something like 33° C?

*Barcroft* Yes, 34° to 35° C is the best

*Montgomery* Would you comment on that for the benefit of all of us?

*Barcroft* Yes Dr Edholm (17) was largely responsible for this choice of temperature His aim was to use a temperature which, so far as possible, maintained all the tissues of the limb at the same temperature as that of the normally clothed limb He therefore measured the temperature at different points in the limb with a thermoelectric needle immediately after the clothing had been drawn away, and he also measured the temperature in the limb when it was immersed in water at a series of different temperatures and he found that water temperature of between 34° and 35° C was best suited to keep the parts at normal temperature

*Montgomery* And higher temperatures than that increase the flow, and lower temperatures than that decrease it?

*Barcroft* That is quite right For instance, at one time Grant and Pearson (18) used a water temperature of 30° C but that cools the tissues and the blood flows obtained at that temperature were subnormal

*Stead* These blood flows, however, are widely affected by ambient temperature If a person gets hot, then the blood flow increases in spite of the sort of neutralizing effect of the local water bath

*Barcroft* Yes, to some extent Spealman (19) has shown that *

*Lamport* Dr Barcroft, would the pressure of the water in the plethysmograph influence the findings? Do you obtain a different result with the air plethysmograph? I gather you sometimes use one type and sometimes the other

*Barcroft* That is right Small differences in the water pressure do not seem to make very much difference

*Burton* I think you should say that that diagram, which is schematic, greatly exaggerates the column of water about the leg, doesn't it? In practice, it is not more than an inch and a half, is it?

*Barcroft* That would be right

*Burton* It looks a lot worse than it is, is that right?

*These comments and references apply to skin flow measured with the hand plethysmograph whereas the method Dr Barcroft is presenting measures principally of blood flow in the skeletal muscle of the calf

using the plethysmograph not on the calf as shown previously but on the forearm The whole setup is essentially the same including the intra venous infusion of the epinephrine You see that during the infusion of epinephrine in this typical case there is an initial large transient dilation lasting about a minute and then after that a much smaller sustained vasodilation which lasts for the remainder of the infusion In this case the infusion has lasted 10 minutes

I do not wish to discuss the reason for these changes at this time but I would like to show you that they are consistent with the plethysmographic technic Table I shows the numbers of the subjects on the left and the other figures are the milliliters of blood flow per 100 milliliters of forearm per minute During the saline infusion the average was 2 7 During the transient vasodilation the flow increased about three times to 9 9 and then it settled down to about double the original value at 5 2 These results are very consistently obtained by this method and Dr Stead can I think substantiate this point because he has also observed this effect

TABLE I

Plethysmograph

| Subject No | Blood flow ml/100 ml forearm min | | |
|---|---|---|---|
| | During saline | During epinephrine 10 μgm min | |
| | | Transient vasodilation | Sustained vasodilation |
| 1 | 1 7 | 8 6 | 3 8 |
| 2 | 3 0 | 9 5 | 5 0 |
| 3 | 3 8 | 11 7 | 6 9 |
| 4 | 3 1 | 9 1 | 7 4 |
| 5 | 2 3 | 11 4 | 3 0 |
| 6 | 2 3 | 8 8 | 4 9 |
| Average | 2 7 | 9 9 | 5 2 |

flow changes markedly as the temperature of the part is changed If the temperature of the tissue is really changed the blood flow changes

*M. Knisely* I did not make myself quite clear For what kinds of physiological purposes is the whole device?

*Barcroft* You mean the whole device of plethysmography? It is simply for measuring the circulation in a part of the extremity in milliliters of blood per 100 milliliters of part per minute, and when it is applied to the muscular parts, like the thigh and the forearm, the results will be mainly those due to muscle When it is applied to the foot and the hand, which are essentially skin, the results will be mainly those due to change in the circulation in the skin

Figure 12 shows the results which Allen, Edholm, and I obtained

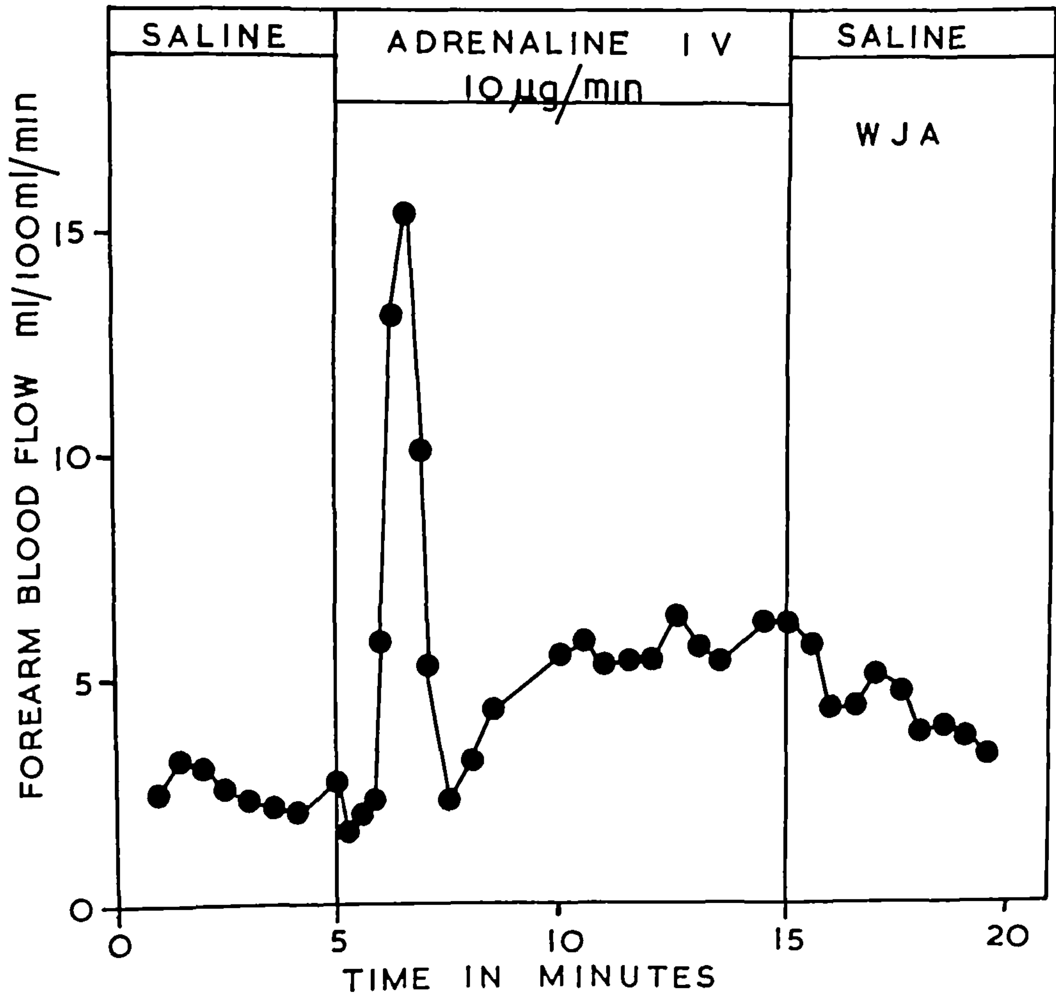



FIGURE 12 Experiment showing the effect of an intravenous infusion of epinephrine on the rate of the blood flow in the forearm There is an initial large transient vasodilation followed by a smaller sustained one The vessels concerned are those in the skeletal muscles

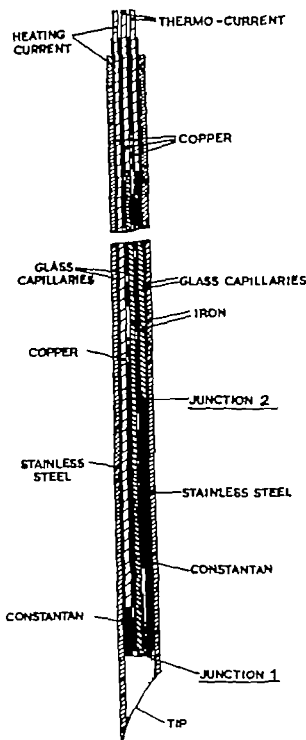



FIGURE 13 Construction of the Hensel thermoelectric needle The tip of the needle is heated by the passage of an alternating current through a short piece of constantan (2 mm.) seen on the left hand side of the lumen The rise in temperature of the tip of the needle is recorded thermoelectrically The test junction (junction 1) is at the tip of the needle, and the reference junction (junction 2) *is 10 mm.* proximal to it. The junction temperature difference is inversely related to the rate of the blood flow the heating current being constant.

*Stead* Yes

*Kety* May I ask what the blood pressure does in these two periods?

*Barcroft* There is a transient fall followed by a very small sustained rise, quite insufficient to explain the sustained increase in flow

*Stead* If this test is made on a person whose blood pressure homeostasis is disturbed by disease of the autonomic nervous system, the arterial pressure falls considerably The reason it does not drop more in normal subjects is because of the activity of the homeostatic mechanisms which tend to keep the pressure stable

B THERMOELECTRIC NEEDLE

*Barcroft* Let us next consider the Hensel (21) needle, shown in Figure 13 This needle is about 0 9 mm wide and perhaps 3 inches long It resembles the Grayson needle in some ways On the left near the tip there is a little black rectangle marked Constantan " That is a heater through which a current is passed to raise the temperature of the tissues by about 3° C

The other dark rectangle on the right is a copper—constantan—copper thermocouple pair Junction 1 is marked at the bottom; this is the test junction and Junction 2 is the reference junction By means of a calibrated galvanometer circuit, the junction temperature difference between those two points can be recorded The junction temperature difference is essentially determined by the heat output of the heater and by the carrying away of the heat by the blood flow The more rapid the blood flow, the smaller will be the junction temperature difference

This has the great advantage over the Grayson (22) needle in that the test junction is situated in the tissue itself I had the good fortune to have Dr Hensel come and work in London, and we carried out experiments to see if we could confirm the results which Allen, Edholm, and I (23) had gotten with the plethysmograph, with the epinephrine infusions The technic we used was to insert the needle into the muscle in the left calf and then to cover the calf over with cotton wool to maintain it at a normal temperature We put the plethysmograph on the right calf and took simultaneous records with the thermocouple needle and the plethysmograph of the changes in blood flow during the epinephrine infusion

Figure 14 shows the averaged results of the six measurements which we made in this way (24) The top of the figure shows the results obtained with the plethysmograph Below are the results for the Hensel needle. There are sustained and transient dilations in both cases The plethysmograph is measuring the flow in the whole of the calf, the needle gives an idea of the changes in blood flow at a particular point

Would it not be useful in this field to begin to use the term clearance of heat because this is really what it is measuring isn t it?

*Barcroft* I am a bad physicist and frankly don t understand the physics of this needle, but I expect you are quite right on that point Dr Burton

*Burton* Another minor point from the historical point of view is this For the record, would you be willing to include the name of Gibbs (25) who in this country was really the first to use this method? This was around 1930

*Barcroft* Yes, I will do that Do you remember exactly where he had his reference junction?

*Lamport* It was very close to the needle tip

*Barcroft* Just like the Hensel needle

*Lamport* Gibbs used direct current as a heater almost at the needle tip which consisted of one of the thermocouples

*Barcroft* Figure 15 *A* to *F* shows the results obtained in the individual experiments

*Lamport* It is noteworthy there that the needle does not go back to the same level that the plethysmograph does

*Barcroft* Yes

*Green* Is the deflection of the needle record due to a decreased temperature difference between the two junctions?

*Barcroft* Yes

*Gregg* Does it make any difference when this needle is in the proximity of small veins?

*Barcroft* Yes it does

*Gregg* How can you tell?

*Barcroft* Dr Hensel carries out a number of tests before he starts recording Among other things he tries the effect of shutting off the circulation in the limb and of seeing what happens during the reactive hyperemia phase and he does this with the heating current on and also with it off But I cannot tell you more offhand

*Cournand* What are the ordinates for the needle? I can see that time is one ordinate but what about the other? How can you compare one tracing with another?

*Barcroft* They are really relative units The junction temperature difference is more or less linearly related to a change in the blood flow The needle is put in and a certain set of results is obtained those are relatively comparable as long as the preliminary test is satisfactory The needle cannot be taken out and put in again nor can the result with the needle on the second occasion be compared with the result on the first occasion

in the muscle It would not be surprising if the agreement between the two, then, was considerably less than it is there and, in fact, we shall see that they do not agree as closely as in the individual cases

*Burton* May I interrupt now on the question of semantics? Would you be receptive to the idea of saying that this method of the needle is really measuring what we could call "heat clearance," just as the radioactive method is measuring a clearance of the radioactive substance?

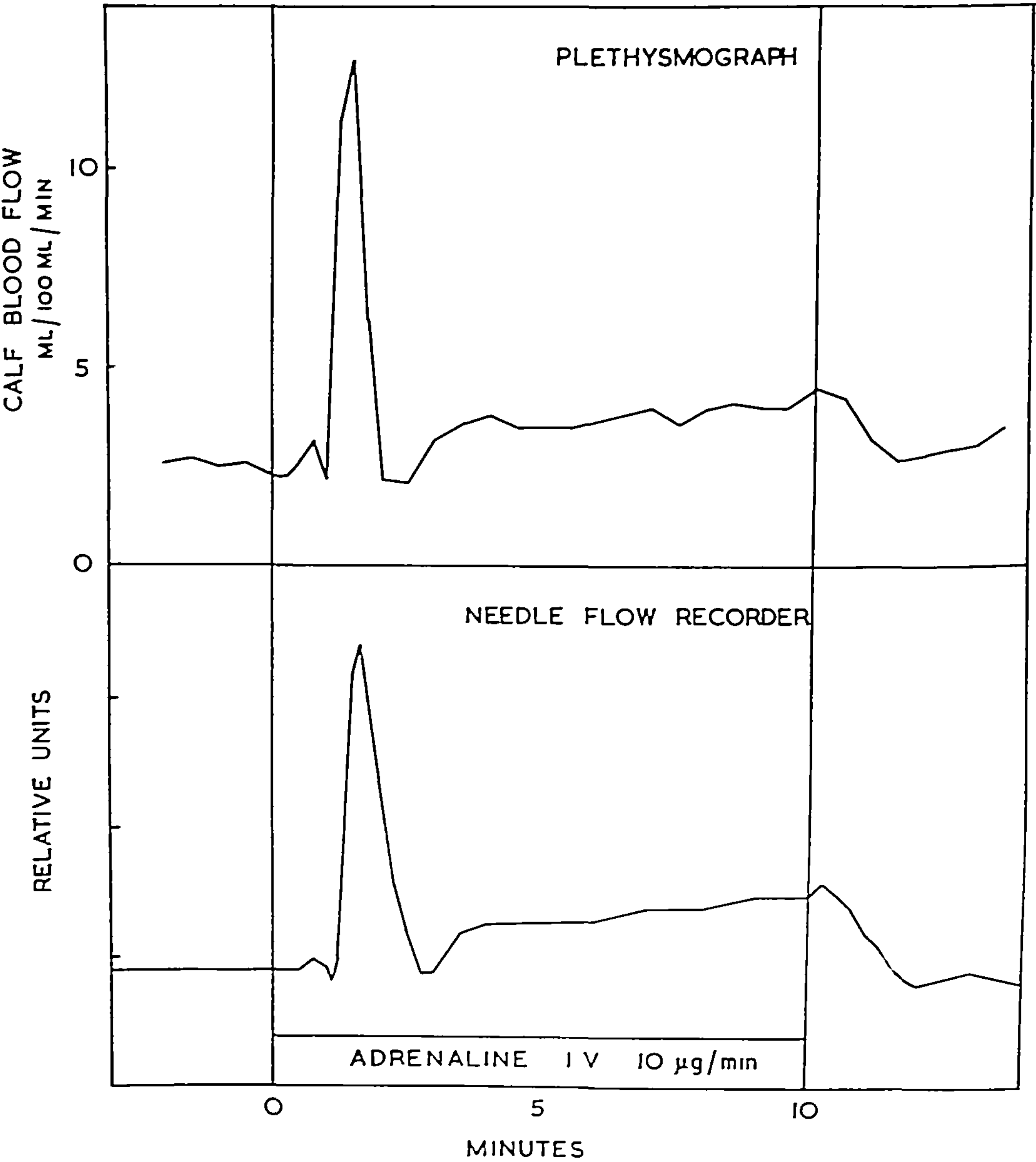



FIGURE 14 Averaged results of six experiments in which the effect of epinephrine on the blood flow in the calves was recorded simultaneously with the plethysmograph and the Hensel needle Transient and sustained vasodilations were recorded by both methods

*Green* Were these done with an ankle cuff on the leg with the needle in place?

*Barcroft* In order to express the deflections in terms of blood flow readings are made with the needle when the flow is shut off and during a maximum reactive hyperemia We know that the flow is zero when it is shut off by a cuff and from the plethysmograph we have a rough idea that the flow will be something like 30 ml /100 ml /min in the calf during reactive hyperemia In this way we can obtain a rough calibration in terms of blood flow

*Burton* Do you know if Dr Hensel takes account of the theory that the calibration is not linear but hyperbolic? Physics shows that this will be so in all these such devices In other words when the flow is very low it is much more sensitive to changes of flow than when it is high Does he take account in his calibration of the fact that that is really a hyperbolic or reciprocal curve?

*Barcroft* His paper would show his theory of the physics

*Burton* Dr Schmidt (26) and I think Dr Kety did a good deal of work with very similar devices on the same principle Dr Kety is it not true that actually all such curves in a calibration are really almost hyperbolas?

*Kety* I would say yes from theoretical considerations but I have had little experience with thermoelectric flow meters As a matter of fact Dr Schmidt who developed a thermostromuhr never had a great deal of confidence in thermoelectrical recording and did not expect to obtain anything but relative values

*Lamport* Dr A M Scher (27) when studying for his doctorate at Yale used the modified Gibbs needle and he calibrated it I believe Gibbs himself had done some calibration and someone else had reported something very similar In looking up my notes on the Gibbs needle which I used in 1941-42 I found an empirical equation, essentially hyperbolic and relating rise in temperature to flow rate this was derived from Gibbs calibration of his needle in the renal cortex of the cat However a logarithmic equation would have fitted as well Dr Gregg and his coworkers (28) had reported a logarithmic relation between flow and temperature rise for the thermostromuhr which is basically similar to the Gibbs needle Log log paper gives a straight calibration line if a full flow method of calibration is used particularly with an artificial system but this was also true of a living one

Scher found that by sticking the needle into sand as an artificial tissue and then perfusing the sand with water he had a good analog of renal tissue to ensure that his device was working properly prior to an experiment Furthermore in this way he did obtain straight cali

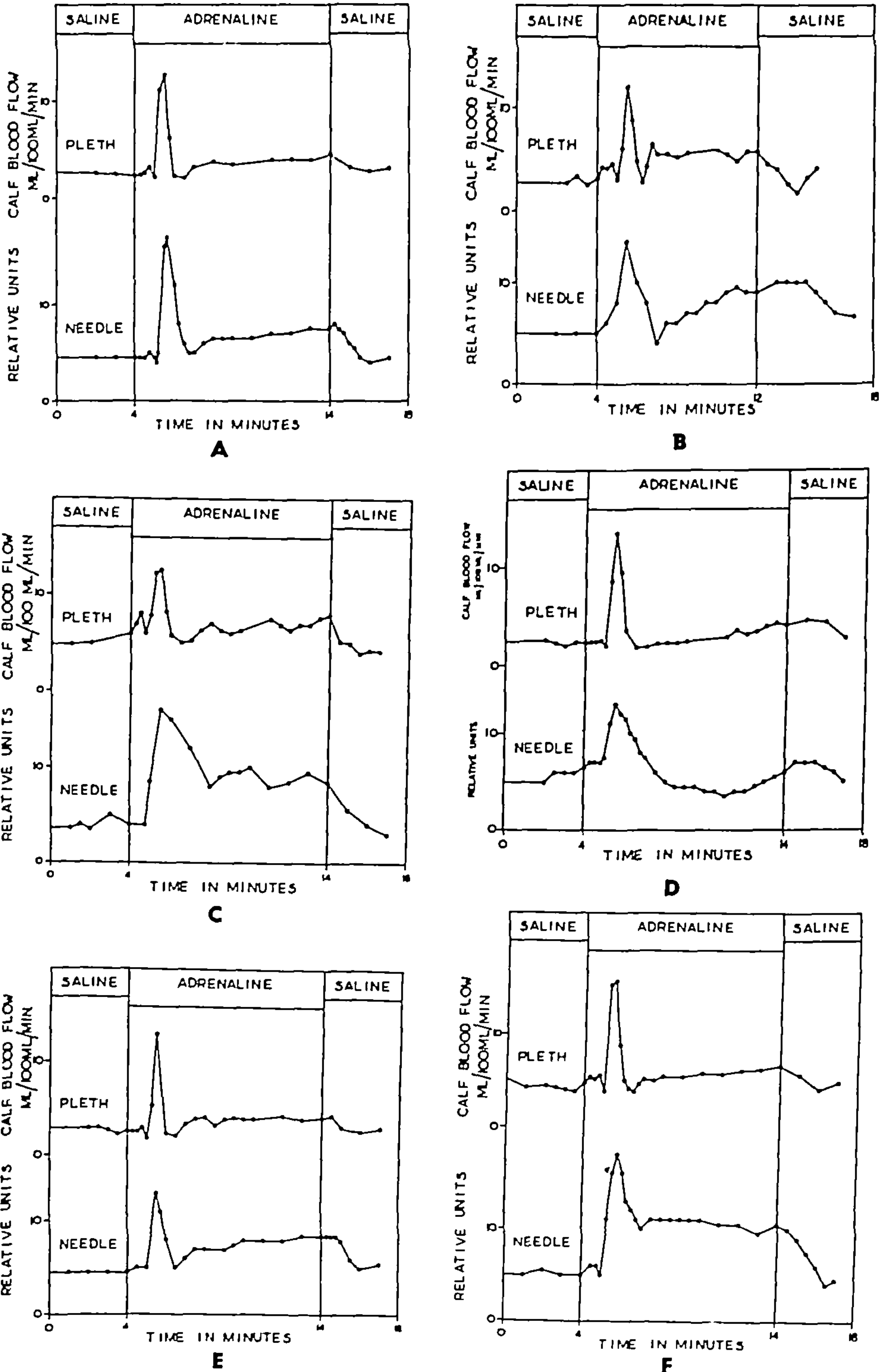



FIGURE 15 Six experiments in which the effect of epinephrine on the blood flow in the calves was recorded simultaneously with the plethysmograph and with the Hensel needle

the epinephrine intravenously and recorded the changes on both sides

The top of Figure 16 shows the sodium clearance results after the injection of about 30 microcuries of radioactive sodium in 0 1 ml of saline into one of the calf muscles

At 30-second intervals throughout the experiment counts were recorded with the Geiger Müller counter After the experiment the

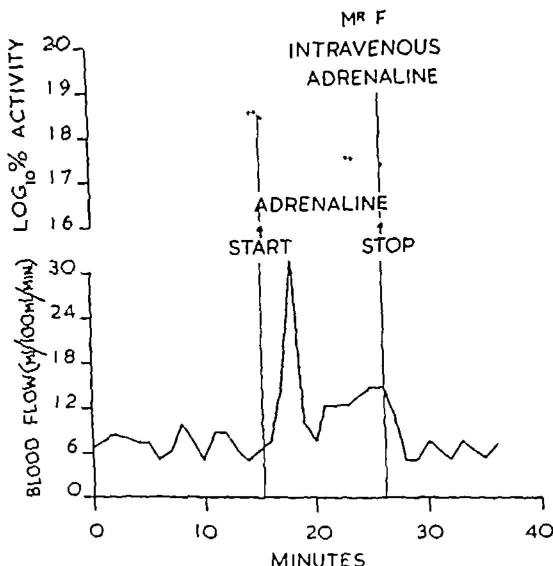



FIGURE 16 Experiments in which the effect of intravenous epinephrine on the blood flow through one calf was recorded with the plethysmograph and its effect on the disappearance of $Na^{24}$ was measured simultaneously in the opposite calf Although epinephrine causes a large transient followed by a smaller sustained increase in the blood flow it had no effect on the rate of disappearance of the $Na^{24}$ Reprinted, by permission, from Walder D N The local clearance of radioactive sodium from muscle in normal subjects and those with peripheral vascular disease *Clin Sc* 12, *153 (1953)*

bration lines on log-log paper, which were found to be valid for experimental application, where relative changes were of prime interest

Calibration at or near zero flow is the most erratic condition for the Gibbs needle There must be a long wait for stability because heat is slowly and steadily building up in the nonperfused tissues, and meanwhile other changes are occurring As a result, zero flow is the least valuable point on the calibration curve Actually, something like a half flow rate is a much better point on the line—for the low end The temperature difference approaches zero as the flow rate rises I can see that in human applications the use of half flow for calibration may be difficult

*Barcroft* Is that with the needle in the tissue or in blood?

*Lamport* Both the heated and the control thermocouples were in tissue

*Remington* Would the flow pattern given by the needle be changed if the thigh was occluded by a cuff to the same pressure as it was in the plethysmograph experiments?

*Barcroft* That was not tried in these experiments, Dr Remington Dr Hensel has told me that the volume of blood in the tissues has scarcely any effect on the deflection It is the rate of the blood flow that counts

*Lamport* This problem is really one of convection, which is rather a standard engineering problem The engineers find empirically that logarithmic curves, which become straight lines on log-log paper, give them good results where convection is involved, and this is why Scher, on my advice, followed their method

*Burton* I wrote about this many years ago (29), and included some rather impressive mathematics, but I think the direct approach is probably much better

*Barcroft* Thank you very much I think that the agreement between the two is certainly quite impressive and has given us confidence that these changes are the ones that did take place in the over-all blood flow in the muscle during the intravenous epinephrine infusions One method supports the other and is in marked contrast now with the results of certain other methods which I shall show you

### C $NA^{24}$ CLEARANCE

Next, I will discuss the results of the radio-sodium method, with which I have had no personal experience and so I will quote first from experiments by Walder (30), who used a technic similar to the one Hensel and I used, and did the sodium clearance in one calf while doing the blood flow by the plethysmograph on the contralateral calf He gave

was 4 2 and the over all average during the epinephrine infusion was approximately double, or 7 5 Those figures were obtained from experiments on the calf

Table III shows the results of some other experiments which were obtained by Miller and Wilson (31) These experiments were made on the forearm In this case only the sodium clearance was measured the blood flows were not done I put them in because they agree with those in Table II in showing that through a wide range of different doses of epinephrine the clearance of the sodium has not been affected by the epinephrine And of course we know that the forearm blood flow must have been showing these two types of vasodilation.

TABLE III

Radio-Sodium Clearance

| Subject No | Clearance before epinephrine | Dose of epinephrine μgm/min | Clearance during epinephrine |
|---|---|---|---|
| 1 | 0 051 | 5 | 0 048 |
| 2 | 0 053 | 15 | 0 041 |
| 3 | 0 048 | 20 | 0 057 |
| 4 | 0 133 | 20 | 0 140 |
| 5 | 0 041 | 25 | 0 055 |
| 6 | 0 064 | 30 | 0 060 |

Reprinted, by permission, from Miller H and Wilson, G M The measurement of blood flow by the local clearance of radio-active sodium *Brit Heart J* 13 *227 (1951)*

D PRESSURE PLETHYSMOGRAPH

*Rate of Tissue Fluid Formation*

At this time I should like to ask you about the results of the rate of tissue fluid formations which agree with the results of the radio-sodium clearance The method which Dr Kitchin (32 33 34) used for measuring the capillary filtration rate was essentially that first devised by Krogh, Landis and Turner (35) Figure 17 shows the pressure plethysmograph on the forearm It must be modified so that it will re

counts were plotted semilogarithmically, and the clearance rates were calculated The rate of disappearance of the sodium was directly proportional to the clearance constant

The rate of clearance of the radio-sodium was uninfluenced by the intravenous infusion of epinephrine, although, on the contralateral side and simultaneously recorded, the typical transient and sustained vasodilations are apparent

Table II summarizes six of Walder's experiments We should consider its consistency During saline, the sodium clearance averaged 0 046 During the epinephrine infusion, it averaged 0 048

There was no distinction made between transient and sustained increase in blood flow, all the blood flow readings were simply averaged So it is clear that the average blood flow before epinephrine infusion

TABLE II

Radio-Sodium Clearance and Plethysmograph

| Subject No | During saline | | During epinephrine 10 μgm/min | |
|---|---|---|---|---|
| | $Na^{24}$ clearance | Blood flow ml/100ml/min | $Na^{24}$ clearance | Blood flow* ml/100ml/min |
| 1 | 0 072 | 4 3 | 0 061 | 7 6 |
| 2 | 0 052 | 3 2 | 0 046 | 7 3 |
| 3 | 0 034 | 4 1 | 0 045 | 8 2 |
| 4 | 0 047 | 2 9 | 0 078 | 6 8 |
| 5 | 0 035 | 3 0 | 0 034 | 3 9 |
| 6 | 0 059 | 3 3 | 0 047 | 7 0 |
| 7 | 0 021 | 8 5 | 0 024 | 11 6 |
| Average | 0 046 | 4 2 | 0 048 | 7 5 |

*Average for infusion period

Reprinted, by permission, from Walder, D N The local clearance of radioactive sodium from muscle in normal subjects and those with peripheral vascular disease *Clin Sc* 12, *153 (1953)*

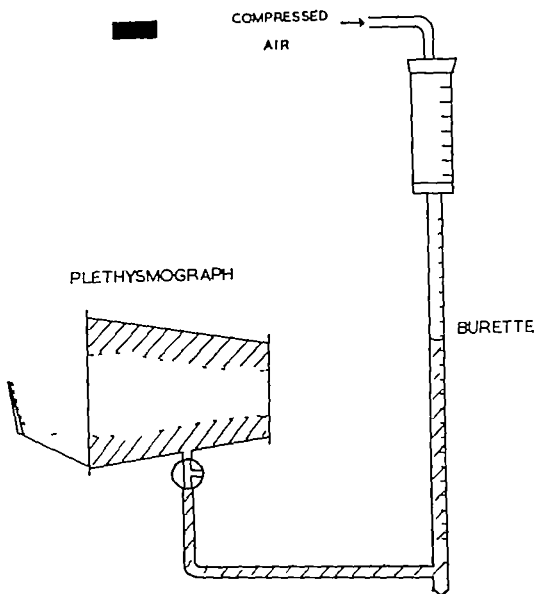



FIGURE 17 Pressure plethysmograph used for the measurement of the capillary filtration rate The apparatus is used as follows The brachial artery is occluded Air compressed to 120 mm Hg is admitted into the burette, drives water into the plethysmograph, and expels blood from the forearm. After 2 min the level of the water in the burette is read (X) The pressure on the artery and on the forearm is released A pneumatic cuff on the upper arm is inflated to 40 mm. Hg to increase the filtration pressure and tissue fluid is collected for 15 minutes The cuff pressure is then released and ½ min. later compressed air is readmitted to the burette for 2 minutes and the water level is read for the second time (Y) Y — X is the rate of tissue fluid formation for the congested segment of the forearm in the plethysmograph for 15 min. It is expressed in ml /100 ml fore arm/min Courtesy of Dr A H. Kitchin, Sherrington School of Physiology St Thomas's Hospital London, England.

main very strictly in one position The figure shows an arm coming out from behind the plethysmograph and resting on the olecranon process so that it is more or less anchored constantly in the same position

The plethysmograph is connected to a U-tube filled with water and a calibrated burette which widens out toward the top To measure changes in the volume of the forearm tissues, compressed air is admitted into the top of the burette, and the blood is expelled from the forearm After 2 minutes, a reading of the level of the fluid in the burette is taken, this figure is the reduced forearm volume If, between the time that reading is taken and any subsequent reading is taken, the tissues themselves have changed their volume, then this change would be indicated by a change in the level of the fluid in the burette

A black rectangle at the top of the figure, which I shall use in the subsequent figures also, marks the period of arterial occlusion compression of the forearm, as I have just explained

At the top of Figure 18 are spots which are readings of the level of the water in the burette The black rectangle is the period of compression, as before The fluid is driven into the plethysmograph and the level in the burette decreases But after an initial rather rapid decrease it begins to flatten out, and after an arbitrary period, which I think is 2 minutes, a reading is taken which represents the reduced forearm volume at that time

*Burton* What must the compression be?

*Barcroft* Dr Burton, the procedure was perhaps a little bit more elaborate than I have indicated The compression was 120 mm Hg and the artery was compressed at the same time

Just to the right of the rectangle at the top, the pressure is released, the forearm swells and the fluid is driven back again into the burette Then there is a second compression and the behavior of the tissue is more or less the same

The question arises as to whether this procedure does really drive out the blood properly Is one measuring the tissues themselves or the tissues plus a variable amount of residual blood? To check on that, Dr Kitchin arrested the circulation in the forearm for something like 5 or 6 minutes, then he released it and, during the height of the reactive hyperemia, when the tissues were full of blood, he put on the compression again Just as much water entered the plethysmograph and the extra blood was all driven out That is a check on the fact that these means are satisfactory ones for driving out the blood What one is concerned with in these measurements is the volume of tissue there plus the fluid in the tissues themselves

*Burton* It started at a higher volume, did it not, in the reactive hyper-

muscle, and so on out of both ends of the plethysmograph by the pressure

*Kety* That height then, does not represent the blood volume of the tissue?

*Barcroft* No it does not The volume of blood in the tissues is only a small part of it

## *Effects of Epinephrine on Rate of Tissue Fluid Formation*

Figure 19 shows how the above method was used to investigate the effect of epinephrine on the rate of formation of tissue fluid The continuous line represents measurements that were made before the beginning of the epinephrine infusion The black rectangles at the top are the periods of measurement of reduced tissue volume After two such measurements the pressure is released and a cuff above the plethysmograph is inflated to 40 mm Hg to raise the capillary pressure somewhat and to encourage the formation of tissue fluid This is the period of venous congestion which lasted 10 to 15 minutes At the end of this period another measurement is made of the reduced forearm volume which shows that the forearm has swollen during the period of venous congestion The amount of swelling can be easily calculated and expressed in ml /100 ml of forearm per min It is the rate of formation of the tissue fluid in the congested forearm After obtaining the above control data the intravenous epinephrine infusion was started and the procedure repeated exactly as before obtaining the results indicated by the dotted line All during that period of venous congestion (the dotted line) epinephrine was being administered intravenously into the elbow vein of the subject and yet when the change in the volume of the tissue fluid was measured at the end of the venous occlusion it was found that even a little less fluid had accumulated in this particular case than had accumulated before the epinephrine was given

*Lamport* How well do the normal controls reproduce themselves? If you put two normal controls on the same figure would they have much closer correspondence?

*Barcroft* The next figure will give you some idea of that Figure 20 shows results which were obtained from six different subjects

*Montgomery* May I interrupt just a moment to make sure that you are dealing here with both muscle and skin?

*Barcroft* That is quite correct

*Montgomery* So this is a resultant of the two as far as changes are concerned?

*Barcroft* Yes that is quite true In Figure 20 are shown the results

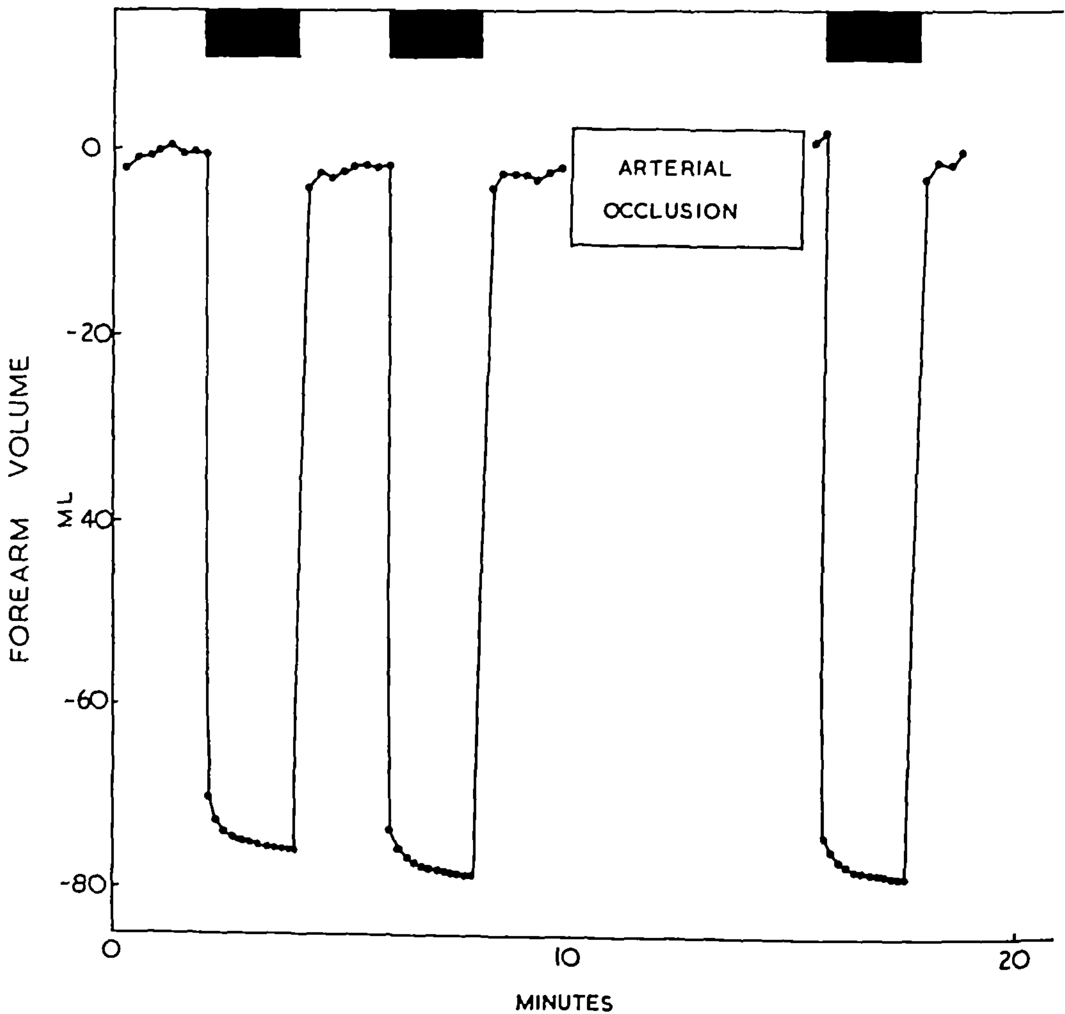



FIGURE 18 Experiment with the pressure plethysmograph showing that the compression procedure drives the blood out of the forearm Black rectangle compression to expel the blood from the forearm (see Figure 17) The forearm volume was measured during compression twice before and once immediately after a period of 5-minute arrest of the circulation in the arm Although the vessels must have been more widely dilated during the period of reactive hyperemia, the subsequent compression appears to have driven all the extra blood out of the vessels Courtesy of Dr A H Kitchin, Sherrington School of Physiology, St Thomas's Hospital, London, England

emia, and actually you drove out more volume but it reached the same base line?

*Barcroft* That is right, yes

*Kety* Dr Barcroft, I should think the differential between the starting point and the final plateau would represent the blood volume, essentially

*Barcroft* I think the main change there is due to the expression of

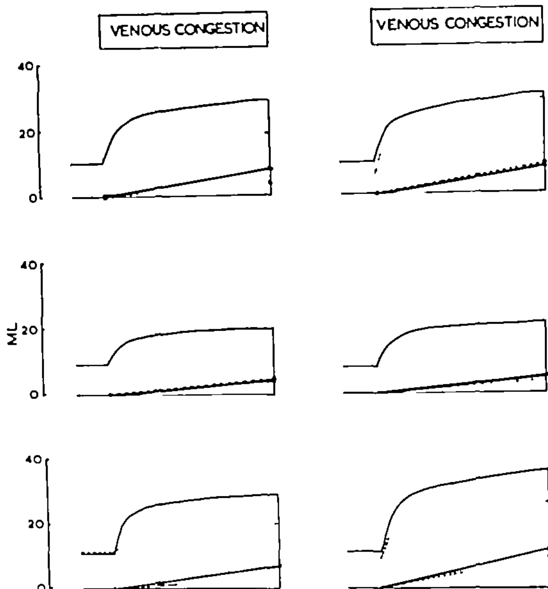



FIGURE 20 Results of six experiments showing that epinephrine had very little effect on the rate of tissue fluid formation in the congested forearm The continuous sloping line at the bottom of each diagram shows the volume of tissue fluid collected during the congestion period before epinephrine was given The broken sloping line at the bottom of each diagram shows the volume of tissue fluid collected during the intravenous infusion of epinephrine Reprinted by permission, from Kitchin A H Observations on the Circulation in Human Skeletal Muscle *Ph D Thesis Univ London* 1955

line represents the increase in the reduced forearm volume during venous congestion while the subject was receiving epinephrine The slopes of these lines are measures of the capillary filtration rates in the congested forearms Notice that the capillary filtration rates obtained during administration of epinephrine (dotted straight lines) are not greater but

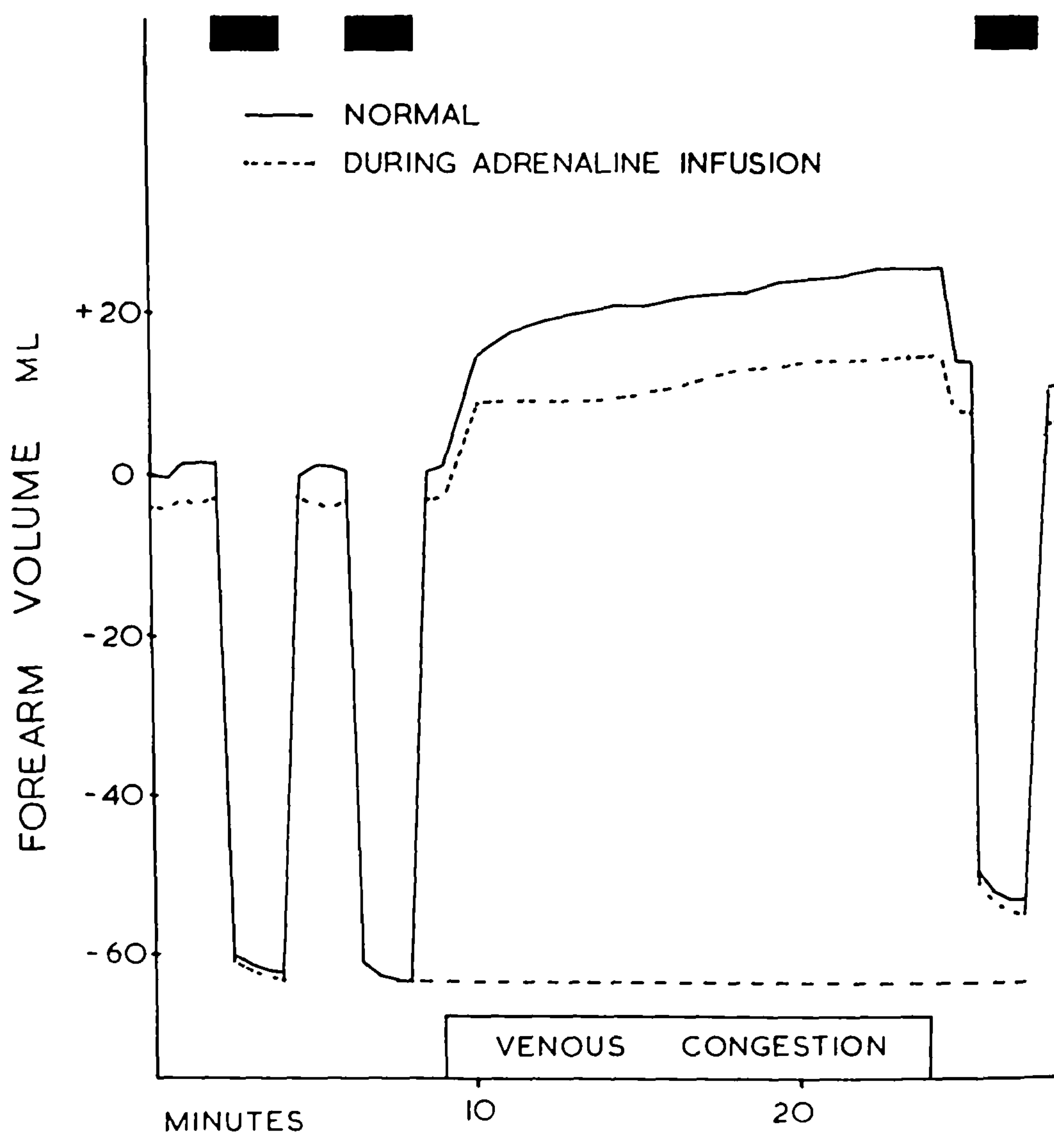



FIGURE 19 Experiment showing the effect of intravenous epinephrine on the capillary filtration rate in the forearm Changes in the forearm volume recorded with the pressure plethysmograph before (continuous line) and during (broken line) intravenous epinephrine Black rectangle compression to expel the blood from the forearm (see Figure 17) The volume of tissue fluid collected during 15 minutes of congestion before the epinephrine infusion was the same as that collected during the infusion Courtesy of Dr A H Kitchin, Sherrington School of Physiology, St Thomas's Hospital, London, England

of six individual experiments We really need not be concerned with the upper pair of curves in each of the diagrams, but only with the bottom pair of lines In each diagram, the continuous straight line represents the increase in the reduced forearm volume during venous congestion before the subject received epinephrine The broken straight

burette to drive water into the plethysmograph and expel all blood from the forearm After 2 minutes the level of the water in the burette was read Call this reading X The pressures on the artery and forearm were then released (2) The cuff surrounding the lower part of the upper arm was then inflated to 40 mm Hg to raise the capillary filtration pressure Tissue fluid was collected for 15 minutes The cuff pressure was then released and half a minute later (3) the brachial artery was occluded and compressed air was readmitted into the burette for 2 minutes and the water level read for the second time Call this Y Y X was equal to the capillary filtration rate during the intervening 15 minutes of congestion The capillary filtration rate was recorded in this way both before and during the intravenous infusion of epinephrine After the experiment the volume of forearm enclosed in the plethysmograph was measured by water displacement and the capillary filtration rates expressed in ml /100 ml of forearm per min

This plethysmograph can be used to measure blood flows by turning the burette off and turning the flow recorder on Figure 21 shows the effect of epinephrine on the blood flow and on the capillary filtration rate, as observed during these six experiments These were not measured simultaneously On the left the ordinate is the result expressed in the percentage of the control level The white column is the blood flow The blood flows throughout those six experiments are all increased about 100 per cent and they are ranging around the 200-per cent mark Those in fact are the levels of the sustained increase in blood flow The transient increase is not taken into consideration in this series of experiments

*Stead* Is this blood flow with the congesting cuff on or without?

*Barcroft* Without The black rectangles show the capillary filtration rates compared to 100 and on the whole they are slightly decreased with epinephrine

In summarizing I would say that the plethysmograph and the Hensel needle agree in showing that there is vasodilation in the forearm and calf during the intravenous infusion of epinephrine and that furthermore, this can be divided into transient and sustained phases The most significant one is doubtless the sustained phase and the flow during that phase is approximately doubled

On the other hand when the sodium clearance method is used either on the forearm or the calf muscle the rate of clearance is not affected during the intravenous infusion of epinephrine The clearance methods of course, are done without any congestion cuff on

However when we measure the capillary filtration rate in the congested forearm, we find that there is no effect of epinephrine on it so

if anything, less than those obtained before the epinephrine was given (continuous straight lines)

*Merriman* What is the line at the very top—the zero line just before venous occlusion? What does that slope signify?

*Barcroft* We are not directly concerned with that but it is interesting and important That is caused by the fact that while the subject is receiving epinephrine, the forearm in the plethysmograph is essentially smaller, and that is because the volume of blood contained in the forearm is less because of the contraction of some vessels

*Burton* Although the blood flow has gone up by the plethysmograph?

*Barcroft* Yes

*Burton* So the arm is smaller but the blood flow is higher?

*Barcroft* Yes

*M Knisely* Does that mean there are arteriovenous anastomoses?

*Barcroft* I suspect that is mainly a venous effect, but I do not know It is a point of interest and one that should be investigated, but what we are concerned with at the moment is the fact that epinephrine does not change the capillary filtration rate in the congested forearm

*W Knisely* Are these lines plotted from only two points?

*Barcroft* That is right

*W Knisely* If more points were obtained, the shape of that curve might be interesting, to see how much of a change takes place early in the congestion or late in the congestion

*Barcroft* Yes, it might be

*Stead* This was a relatively constant capillary pressure in both situations, since you had a cuff around the arm inflated to 40 mm Hg?

*Barcroft* That is so, yes

*Stead* And also it would have meant that most blood vessels dilated If you put the skin at the level of 40 mm Hg most of the vessels in the part will dilate, so in both systems there were vessels which were not normally filled Is that right?

*Barcroft* That is perfectly right It is certainly not the capillary filtration rate in the normal tissues It is the capillary filtration rate in the congested forearm

*Green* Was the occlusion cuff pressure, that is, the pressure proximal to the plethysmograph, left elevated at the time you applied the compression pressure in the plethysmograph? In other words, did the pressure on the blood in the plethysmograph have to drive the blood out against the occluding cuff pressure?

*Barcroft* The steps were as follows (1) The brachial artery was occluded by the inflation of a cuff on the lower part of the upper arm Air compressed to 120 mm Hg was admitted into the upper part of the

thus passively increased filtration of fluid into the tissues might be increased at the same time that the blood flow through the part was increased

*Kety* Dr Barcroft s observations were also upon the effect of epinephrine without venous occlusion You remember those first two trials before venous occlusion in each case and the dotted line of epinephrine showed the same residual limb volume as occurred normally

*M Knisely* I would like to define the problem that Dr Barcroft presented He has two systems of measurement of blood flow which essentially agree very well Then if I understand correctly radioactive sodium has been put into the muscle with a needle I am an histologist and I have made many studies of living muscles under the microscope Much of this work has been done in Professor August Krogh s laboratory One can only guess but the guess that seems most probable is that the fluid did not get out into a vascular system at all It was probably put out into spaces between striated muscle fibers and perhaps around connective tissues

Another seemingly worthwhile guess is that there are two factors which limit the rate of movement of the sodium out of the whole gross anatomy of striated muscle One might be the rate of passage of the molecules into the vascular system and the other might be the rate of flow The limiting factor is probably the rate of diffusion into the vascular system including the rate of movement out possibly by way of the lymphatics

We are dealing with a system limited by the motion of the molecules into the vessels much more than by the rate of flow through the vessels In our laboratory we would not consider the sodium method at all as a measure of flow

*Kety* There are two puzzling features about what Dr Barcroft has said In the first place the relationship between the sodium clearance value and the resting blood flow as measured with plethysmography and secondly the relationships under the influence of epinephrine I believe the average clearance constant was 0 046 in one of the series and the plethysmographic blood flow was 0 042 expressed as ml /ml /min. But that of course, is a misleading coincidence since the clearance constant it can be shown, is related to the effective blood flow per unit of sodium space of the tissue

Since the sodium space of the tissue is roughly 20 or 25 per cent, a value of 0 046 for the sodium clearance should be multiplied by 25 per cent which would give us a value of a little over 0 01 for the effective blood flow as measured with radioactive sodium if one chooses to ignore for a moment the diffusion phenomena, which of course is an extremely

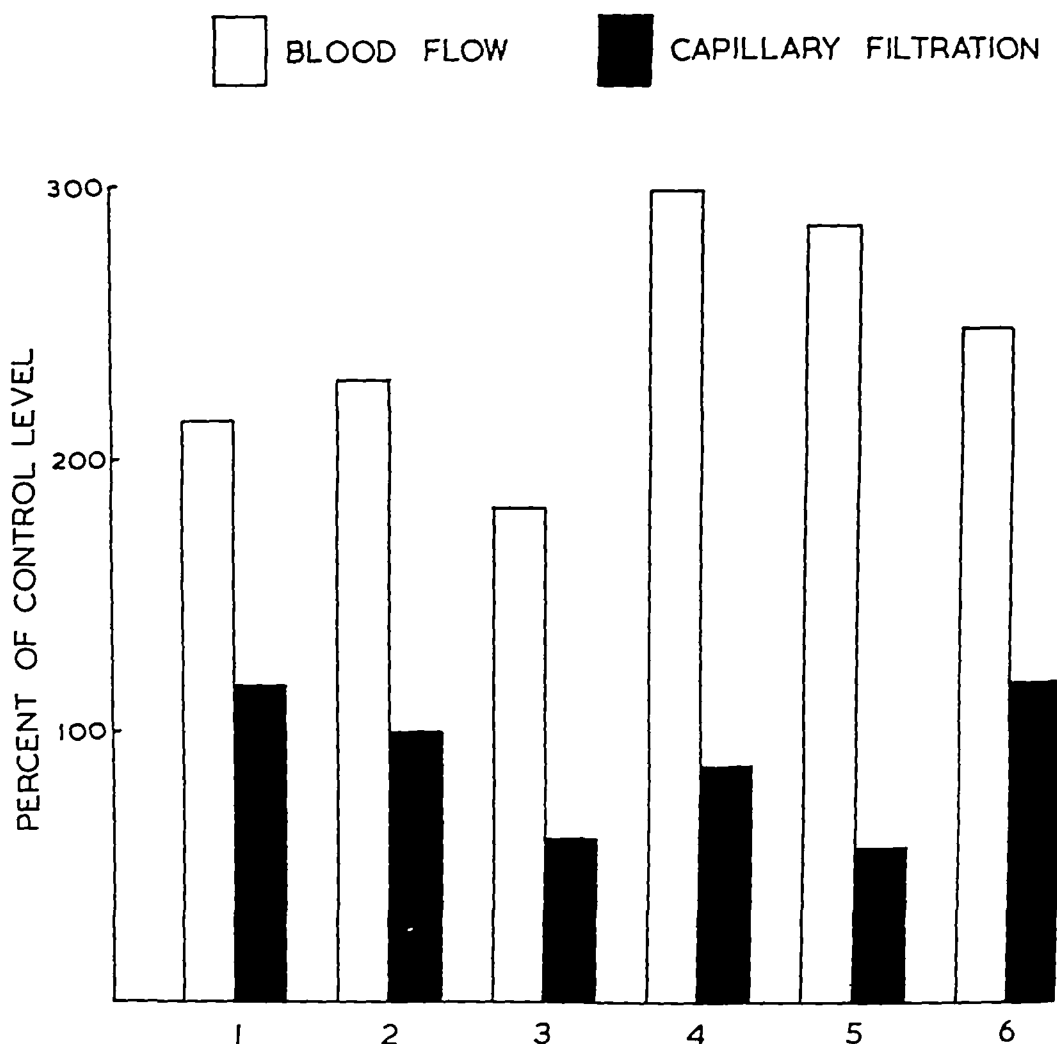



FIGURE 21 Results of six experiments showing that, although epinephrine increased the rate of the blood flow in the forearm, it did not increase the rate of tissue fluid formation in the congested forearm Courtesy of Dr A H Kitchin, Sherrington School of Physiology, St Thomas's Hospital, London, England

there is the sharp contrast between the plethysmograph and the Hensel needle results, showing increase in blood flow, and the results of the sodium clearance and the capillary filtration, which indicate that there is no change in the clearance of fluid or in the rate of capillary filtration I should be most interested to hear any comments on this

GENERAL DISCUSSION

*Stead* Dr Visscher (36) has recently shown that the pressure in the small veins may be increased by a variety of stimuli If epinephrine actively increased the small vein pressure and the capillary pressure was

observations of capillary density in muscle diffusion equations have been set up (38) which indicate that the time for diffusion equilibrium to the extent of 95 per cent between blood and a tissue with the inter capillary distances of muscle would be a fraction of a second and probably not greater than one or two seconds in any case

A time constant of the order of one or two seconds is negligible in comparison with the time constant of several minutes for the circulatory phenomenon

I have injected radioactive gas in solution into a muscle and have gotten essentially the same type of time constants for the clearance

*Burton* Also iodine has been used by others and it produces the same results

*Kety* Except that iodine is an ion which might behave in a similar way but gases diffuse through the whole capillary membrane Krogh did show that diffusion through tissue or through gelatine may not be the same as free diffusion through water but he found only a 50 per cent attenuation of the diffusion coefficient so that even if the diffusion equilibrium time were doubled it would still be insignificant in comparison to the very slow time constant of the blood flow

However even for sodium which may diffuse only through a small fraction of the capillary wall Pappenheimer (40) has calculated that the rate of transfer of sodium across the capillary is about 80 times the rate at which it is brought to the tissue Now Krogh may have been counting capillaries all of which are not open at any one time or the capillaries may be bunched together and not evenly dispersed through the tissue, so that the intercapillary distances may be considerably greater than the estimates which I have calculated from Krogh s observations with a resultant increase in the importance of diffusion

There is however a good deal of experimental evidence (41) to indicate that the uptake of different inert gases by muscle is the same regardless of the molecular weight and therefore the diffusion coefficient of the gas making it unlikely that I have underestimated diffusion limitations within the tissue This brings us to the next point which is the possibility that the injected radioactive sodium does not disperse itself throughout the extracellular fluid as the theory assumes but simply localizes itself in a pocket under those circumstances Then, of course we would be dealing with a diffusion problem of an entirely different order of magnitude and one which could certainly be a limiting factor

*W Knisely* What is the order of magnitude of the volume you introduce?

*Kety* The volume varies from 0 1 ml to as much as 0 5 ml

*W Knisely* Do you obtain a difference between the two?

low blood flow as contrasted with the plethysmographic blood flow which was between 0 04 and 0 05

Before we consider the effects of epinephrine, let us ask the possible reasons for this initial discrepancy The plethysmographic measurement does encompass some skin but I doubt that the blood flow through the skin, under most circumstances, is of enough significance to affect this value for very much so we may probably accept such values as fairly reliable measures of total blood flow to a large mass of muscle

When I first proposed the sodium clearance technic in 1949 (37), I was very careful to point out that it did not measure total *blood flow* in tissue but rather "circulatory *effectiveness*" or the ability of the circulation to remove and to supply diffusible substances If I were a tissue cell, I think I should be more concerned about the value of this function than the mere quantity of blood flowing past me In any case, I derived an expression for this clearance constant, k, relating it to blood flow and to a "fudge factor," $\theta$ $k = F\theta$ The latter factor represented those functions which would tend to limit complete equilibrium between tissue and vascular bed and included shunts and diffusion limitations

The first possible cause of the discrepancy between clearance and plethysmographic values, and the one which I think actually is the most important one, would be the presence of shunts which the plethysmograph would measure and which the sodium clearance would ignore To what extent shunts may explain these phenomena, I do not know

*M Knisely* I have studied striated muscle extensively, at various times in 1936, and I have never yet seen an arteriovenous anastomosis in a gross anatomical striated muscle during life There is pure, straight evidence I have not yet seen it

*Stead* Did you give them epinephrine?

*M Knisely* No

*Kety* Let us now consider the question of diffusion, since we have ruled out the question of shunts *

*M Knisely* Not ruled out, sir, just negative evidence so far

*Kety* In the past 10 years, I have done some thinking and reading about the problem of diffusion in tissues (38) and, although I have not yet come to a categorical conclusion, neither can I find much evidence to support Dr M Knisely's guess that diffusion is the limiting factor in the phenomenon under discussion On the basis of Krogh's (39)

* Addendum by Dr Kety Dr Zweifach, however, has fairly definitive evidence which he presents later for the presence of moderately large arteriovenous shunts in skeletal muscle through which most of the blood flows during rest If this evidence is correct, it is capable of explaining most if not all of the discrepancy between the sodium clearance and the plethysmographic data

and his colleagues perfused the striated muscles Following each experiment they injected a black pigment into the vascular system then removed the skin from the muscles to be certain that they had been studying muscle circulation and not some combination of muscle plus skin

In 1948 we reviewed the circulation through muscle and added some observations (46)

Dr Kety I would like to hear your explanation of the difference between the plethysmographic records and the sodium records

*Kety* I feel personally that shunts would be a very reasonable explanation

*Stead* You do not believe that changes in capillary pressure can account for it?

*Kety* I will soon get to your question Dr Stead A net outflow from the capillary as the result of outward filtration would be so slow that it could not significantly affect the entrance of sodium Hyman and his colleagues (47) have indeed shown that a net filtration of fluid from capillaries does not affect the sodium clearance

The lymphatic flow which is incorporated in the clearance constant is not a very significant factor in resting muscle and in any case would not explain why the sodium clearance is too low

*M Knisely* One more possibility These spaces that spread out between muscle fibers by and large have enormous surfaces of collagenous connective tissues fiber surface membranes Is there any evidence that the sodium may remain in or on the collagenous connective tissue fibers? Is that a fair guess?

*Kety* Yes it certainly is Our group has found that the injection of hyaluronidase along with the radioactive sodium increases the rate of removal of the sodium from the tissue this would be compatible with your thesis that the sodium was compartmentalized in an extracellular gel

*M Knisely* The connective tissue has a ground substance as another item to worry over

*Montgomery* What is the order of magnitude of that?

*Kety* The clearance constant went from 0 040 to 0 058 per min. but we do not know the effect of hyaluronidase on local blood flow unfortunately so we cannot really be sure to what extent this effect of the hyaluronidase confirms your thesis of a local trapping of sodium

In addition to a consideration of all possible criticisms of the sodium clearance technic perhaps I may be forgiven if I summarize some of the arguments in its favor In the first place it does change to a considerable extent in response to what are commonly regarded as alterations in tissue blood flow Arterial occlusion causes it to fall to zero

*Kety:* Yes However, the difference is slight and not at all what would be expected on the basis of this supposition Dr Sokoloff,* in our laboratory, made a very careful study of the difference in clearance rate in subjects who had been injected with 0 5 ml and with 0 1 ml He obtained mean values for the clearance constant of 0 051 and 0 040 for 0 1 ml and 0 5 ml respectively, a difference which is statistically significant

If the sodium ion were being removed from a nonvascular injection depot, one would have expected a much greater effect of injection volume

Another observation which, as far as I can see, practically rules out the possibility of a local nonvascular deposit is that Bauer and his colleagues (12) have injected the radioactive sodium by means of a "hypospray" which gets the solution through the skin in the form of a high-speed and very fine jet without forming an appreciable pool Their normal data yield a clearance constant of 0 05 which is exactly what we obtain with 0 1 ml by needle This group also found a considerably smaller clearance constant (about 0 03) when a radioactive ion ($I^{131}$) was injected in a volume of 1 ml On the basis of these data and those of Sokoloff, we can say that there is no evidence for "pooling" of the injected material with volumes of 0 1 ml, but evidence of significant pooling where the volume injected is 0 5 ml or greater

*W Kinsely* What animal was used in these experiments, and what muscles, and did you obtain a difference from one muscle to another?

*Kety* Most of these observations were in human gastrocnemius Dr Sokoloff studied the clearance constant in different parts of the same muscle and in the same muscle of both legs He found minor differences but, in general, the clearance through muscle seems to be reasonably constant

*M Knisely* Dr Kety, a pathologist by the name of J N P Davies,† from Uganda, points out that, "Differences must be explained somehow" This is now one of the most essential moments in the history of science We have an "indicator" The fundamental problems are to test the indicator, to validate it, and to learn under what circumstances to use it and when not to use it There are extremely marked differences between the curves of the plethysmograph and the results of this new method, and the plethysmograph curves agree, according to my memory, with the results of studies by Anrep and his colleagues (43, 44, 45) on the circulation through striated muscles During these studies, Anrep

*Sokoloff, L Study of regional circulation by the clearance of radioactive sodium (Unpublished data)

†Prof Davies is a member of the Dept of Pathology, Makerere College Medical School, Mulago Hospital, Kampala, Uganda, East Africa

the paradoxical experiments reported by Dr Barcroft is not enough to permit reaching a conclusion I am therefore substituting an analysis I made subsequently since it seems to lead to conclusions that may aid in resolving the paradox of the effect of epinephrine in doubling of blood flow rate in the forelimb without change in capillary filtration during venous congestion or in radioactive sodium clearance

I shall make many simplifying assumptions which I believe are justified First I shall assume the applicability of Poiseuille s law in the postarteriolar circulation which seems reasonable since Pappenheimer and Soto-Rivera (52) found this to be true of the capillary to vein (starting at the effective mid point of the capillary) circulation in the isolated hindlimb of the cat I shall assume that the viscosity and hematocrit of the blood are not materially affected by any of the procedures Dr Barcroft reported and that the blood flow doubles because of epinephrine with the 40 mm Hg venous congestive cuff inflated as compared to the similarly congested control even though no measurements of blood flow with heated needle or plethysmograph in the congested condition were actually made

Since Pappenheimer Renkin and Borrero (53) found that capillary ultrafiltration of plasma was proportional to the difference between mean effective intracapillary hydrostatic pressure and effective plasma osmotic pressure (allowance for the slight protein content of interstitial fluid is negligible here and they found interstitial pressure in animals to be unimportant) Starling s Law is assumed The mean osmotic pressure of plasma as it is concentrated during congestive filtration and the mean intracapillary pressure are both used to approximate the integrated result of progressive filtration of plasma in its course through the capillaries of the congested forearm

Although elsewhere in the discussion at this conference the effect of increased filtration rate on tissue pressure in man was disposed of as negligible, and while there is evidence that this is fairly true for the hindlimbs of cats and dogs (53) there is good evidence reported by Landis and Gibbon (54) that, in man s forearm which is under consideration here increasing tissue pressure becomes an important factor in venous congestion At 44 mm Hg venous congestion it was found that the over all filtration rate for the 8 minute period from the seventh to the fifteenth minute declined 30 per cent from its over all value for the first 6 minutes However we shall base our analysis on the early part of the venous congestion period, assuming that the filtration rates for epinephrine and control were equal at the beginning as well as for the whole of the 10 to 15 minutes of venous congestion referred to by Dr Barcroft

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Let $P_o$ = osmotic pressure of plasma *in vivo* = 95 per cent of *in vitro* osmotic pressure (32)

$P_{oC}$ = effective osmotic pressure of plasma in capillaries of forearm during congestion

$P_{oA}$ = same as $P_{oC}$ except with the influence of epinephrine added

$P_C$ = mean effective intracapillary pressure during congestion

$P_A$ = same $P_C$, except with the influence of epinephrine added. The subscript A instead of C indicates that epinephrine (adrenalin) was used

$F_C$ = filtration rate of congested forearm

$I_C$ = blood flow rate in congested forearm of blood of hematocrit assumed to be 50 per cent

$I$ = blood flow rate in normal forearm of blood of hematocrit 50 per cent

$R_C$ = resistance of capillary vascular system from point in capillaries, corresponding to $P_C$, to the large veins of the forearm during congestion

$A_C$ = filtration coefficient per mm Hg pressure difference of congested forearm

[1] $F_C = A_C (P_C - P_{oC})$ This represents our statement concerning Starling's law

$F_A = A_A (P_A - P_{oA})$

[2] $F_A = F_C$ This was reported by Dr Barcroft

[3] $I_A = 2I_C$ This was also reported by Dr Barcroft and has been discussed

$$[4]\quad \frac{P_{oC}}{P_o} = \frac{I_C}{I_C - 2F_C}, \qquad \frac{P_{oA}}{P_o} = \frac{I_A}{I_A - 2F_A}$$

These equations are true because (*a*) the hematocrit at 50 per cent was presumed not to have changed, (*b*) the osmotic pressure of plasma is proportional to the concentration of water in plasma for small changes, and (*c*) the value of $P_{oC}$ is estimated to be the same fraction of the total increase in plasma osmotic pressure in the capillaries as it is when epinephrine is used The latter point has already been touched on and can be proven in greater detail

[5] $P_C - 40 = I_C R_C$, $P_A - 40 = I_A R_A$ These equations express Poiseuille's law and the definition of resistance

Algebraic manipulation of these equations yields

$$[6]\quad \frac{P_A - 40}{P_C - 40} = 2\ \frac{R_A}{R_C}\quad \frac{A_A}{A_C}\quad \frac{P_A - P_{oA}}{P_C - P_{oC}},$$

$$[7]\quad \text{and } \frac{P_{oA}}{P_{oC}} = \frac{2\,P_o}{P_o + P_{oC}}$$

Unfortunately I do not have Dr Barcroft s figures for blood flow rates in the forearm with or without congestion I believe no such measurements were made with venous congestion Still it is quite reasonable to estimate these quantities since variations in them will be seen to be of small importance

For the circulation from artery to vein we shall use a modification of Poiseuille s law (we deduct 14 mm Hg from perfusion pressure) substantially as outlined in Fulton s Textbook of Physiology (55) Since the hindrance of the capillary to-vein circulation is not changed materially by elevating venous pressure (52) if we assume a normal uncongested venous pressure of 9 mm Hg and a mean arterial blood pressure of 100 mm Hg the following equation results

$$\frac{I_c}{I} = \frac{100 - 40 - 14}{100 - 9 - 14} = \frac{46}{77} = 0\ 60$$

A reasonable rate of blood flow in the normal resting forearm is 2 4 mL/min /100 ml forearm the value we choose for I (56) Allowing for the factor 0 6 just computed would give a blood flow rate during congestion of 1 44 ml /min /100 ml congested forearm We estimate from Landis and Gibbon s paper (54) that a filtration rate of 0 14 ml /min /100 ml forearm for the 40 mm Hg congestion would be reasonable for the first 6 minutes when tissue pressure has risen little Substitute this value for $F_c$ and 1 44 for $I_c$ in equation [4] The osmotic pressure *in vitro* of human plasma may be taken as 25 mm Hg which would give an *in vivo* value for P of 23 3 mm Hg (52)

The value of $P_{oc}$ becomes 28 9 mm Hg from equation [4] so that $P_v$ = 25 8 mm Hg from equation [7]

Equation [6] now becomes

$$[8]\ \frac{P_A - 40}{P_V - 25\ 8} = 2\ \frac{R_A}{R_C}\ \frac{A_A}{A_C}\ \frac{P_C - 40}{P_C - 28\ 9}$$

$$\text{Or where } q = 2\ \frac{R_A\ A_A}{R_C\ A_C}$$

$$[9]\quad P_V = 40 + 14\ 2q\ \frac{P_C - 40}{(1 - q)\ P_C + 40q - 28\ 9}$$

We now estimate $P_C$ from $p_C$, the corresponding value of normal forearm intracapillary pressure without venous congestion Corresponding to equation [5] for congestion the uncongested values are

[10] $p - 9 = IR_C$

Since $I_c = 0\ 61$ we have from equation [5]

$P_C = 40 + 0\ 6\ (p_c - 9)$

Normally, there being no net filtration from capillaries, $P_c$ will be slightly greater than $P'$, effective plasma osmotic pressure, which we have taken at 25.5 mm Hg. We therefore estimate $P_c$ at 24 mm Hg, which yields

$P_c$ 10 mm Hg

Equation [9] now becomes (where $Q = 1/q$)

$$[11] \quad P_A = 10 + \frac{128}{20.1Q - 9}$$

Since $P_A \geq P_c$, 10, the maximal value for Q is 1.16. And $P_A$ is not greater than diastolic pressure (80 mm Hg), since if it were, blood flow would not be maintained throughout the cardiac cycle. Therefore the minimal value of Q is 0.96. Such a range of Q yields

$$0.13 < \frac{R_A}{R_c} \cdot \frac{A_A}{A_c} < 0.32$$

We know that epinephrine constricts the veins to some extent so that $\frac{R_A}{R_c} > 1$. This would then suggest that $\frac{A_A}{A_c} < 0.5$ and that it may be less than 0.13.

The special value of the sodium clearance study lies in that it complements the other observations and permits us to extend our tentative conclusions. Filtration is relatively unimportant as compared to diffusion in the migration of sodium ions (52) so that hydrostatic pressure is uninfluential in their transport to and from tissues in contradistinction to water. Since sodium ions have perhaps 85 per cent of the capillary pore area for diffusion available to them, as is functional for water filtration (52), any factor affecting the filtration coefficient of water would in great likelihood also affect the clearance of sodium. Since the clearance of sodium is primarily dependent on the blood flow rate through sodium-permeable capillaries, one is impelled to explain the constancy of sodium clearance in the face of doubled blood flow during the administration of epinephrine as being caused by a halving in the relative effective sodium diffusion coefficient of the capillaries. Accepting, then, that $A_A/A_c \approx 1/2$, we have

$$0.86 < \frac{R_A}{R_c} < 1.04$$

This lack of indication of a considerable increase in postcapillary resistance (hindrance) as a result of epinephrine is at variance with other observations, epinephrine is known to constrict veins and venules

Possibly $A_v\ A_c > 1/2$ or the constriction of the venous system is not considerable or our assumptions are somewhat at variance with the facts

Whether the change in filtration and sodium diffusion coefficients required by this appraisal actually occurs in the capillary walls is problematical $A_v/A_c$ would also decline as suggested here if most of the blood flow increase resulting from epinephrine were passed through vessels of low effective permeability to water and sodium ion Such vessels might have low permeability either intrinsically because of few pores or because of being short in length Dr Zweifach s comments on the anatomy of the arteriovenous channels he has seen in striated muscle would be quite consistent with this interpretation of Dr Barcroft s provocative paradox

*Remington* How can you assume a constant hydrostatic pressure when the arterial pressure is still normal?

*Lamport* I feel that the venous cuff here must reflect its pressure back very quickly

*Remington* But this is a circulating system with maintained arterial pressure and arterial-capillary gradient

*Lamport* The rate of capillary filtration is measured with the venous cuff on so that means it is being measured with 40 mm Hg capillary pressure, essentially and even reflected into the arterial system

*Burton* As I understand it from Landis original experiments (35) (and Dr Barcroft would verify this) Dr Barcroft was working down near the origin of the curve The swelling will go on continuously and hasn t any sign of slowing up for half an hour has it?

*Barcroft* That is true

*Burton* So we are really working near the origin

*Lamport* I didn t know that, and in that case I would say I do not find that it is really paradoxical

*Moe* Do we know what the blood flow in the muscle is with and without epinephrine when the congestion cuff is on and inflated? You measured congestion during inflation as well as without it didn t you?

*Barcroft* Yes The flow was measured with epinephrine without congestion

*Moe* That is right you couldn t measure flow while the congestion cuff was inflated

*Barcroft* That is right

*Moe* I am making these remarks in support of Dr Remington s point that the circulation is not totally interrupted blood is not running into the extremity without escaping from it As the venous pressure of 40 mm Hg is overcome blood will escape from the limb

nection between the arterial and venous vessels is less common During periods of relative muscle inactivity a large part of the blood from the arterial arcades returns to the venous system without entering the muscle fibers proper These muscle fibers are supplied by extremely short muscular arterioles which penetrate the tissue at right angles and abruptly break up into as many as six to eight capillary branches Precapillary sphincters are encountered at this point of abrupt capillary branching but not as regularly as in the mesentery skin or urinary bladder The capillary blood flow through the muscle fibers proper is sporadic and can be seen to vary with contractions of the short muscular arterioles The capillaries are distributed between adjacent muscle fibers along their length and frequently join one another and then further distally branch again before entering the venous collecting system The blood flow in the collecting venules is exceptionally rapid usually as a consequence of blood coming through capillary channels from the arterial arcades

The distinction on a functional basis between what might be termed surface muscle circulation and internal tissue circulation becomes readily apparent when hemorrhage is instituted The withdrawal of as little as 1 per cent of body weight results in an immediate closure of the muscular arterioles so that the entire mass of capillaries becomes static A rapid flow persists through the arterial arcades and venous interconnections These vessels do not show active contraction unless the pressure is lowered below 50 mm Hg

The surface vessels and the more internal vessels do not react in the same way to vasoconstrictor substances For example epinephrine injected intravenously (1 0 to 2 0 μgm ) will cause a greater narrowing of the venous channels than of the muscular arterioles and will have no effect on the muscular arterioles or precapillaries Arterenol injected intravenously affects primarily the arterial vessels including the muscular arterioles There is further evidence to indicate that this differential reactivity can be altered by local conditions such as occur during muscular exercise

With reference to the clearance of radioactive substances injected into skeletal muscle several relevant remarks should be introduced Although 0 1 ml represents a comparatively small volume on a macroscale this volume of fluid is of considerable magnitude relevant to the small blood vessels With micromanipulative technics it is possible to introduce as little as 0 001 ml and even these amounts are disproportionately large in comparison to the vascular structures In skeletal muscle the injected mass distributes itself between the muscle bundles and is not regularly associated with any particular set of capillary vessels

as high as 90 mm Hg Precapillaries in the mesentery or the surface of the urinary bladder will close only below a pressure of 50 mm Hg

*Nickerson* To return to the question of sodium clearance it seems to me that even with a very fine needle the length of the bevel would be as large as the bundles of muscle fibers containing the capillaries we are discussing I think we can assume that the fluid we are studying in radio-sodium clearance is all between bundles not in the bundles

*Zweifach* I would surmise that the size of the drop introduced by a fine hypodermic needle into the skeletal muscle is as large and perhaps larger than the muscle bundles in which the majority of the blood capillaries are contained

*M Knisely* It is like shoving a crowbar into a lace curtain

*Wilkins* Can we have a little more detail on the channels that lead directly from the arteries back to the veins? You said they were not short shunts Can you say a little more about that?

*Zweifach* Because of the frequency with which anastomoses exist in both the arterial and venous sides of the bed it is frequently difficult to establish clearly whether the capillary blood supply originates from the arterial vessels only Our evidence at present would appear to indicate that none of the capillary vessels have their blood distributed from venous sources The significance of the system of arcades remains speculative They may represent a method of achieving a uniform blood pressure throughout the various branches of the terminal vascular bed

*Wilkins* You mean that a branch can go from one of the arcades directly into a vein?

*Zweifach* The venous portion of the system is fed by capillaries some of which originate directly on the arterial arcades Along the edges of the muscle bundle many of the capillaries fuse to form a single collecting channel which then traverses the surface of the muscle bundle to collect other similar venous capillaries These vessels, which vary in diameter from 40 to 100 microns interanastomose with one another The pattern is highly reminiscent of that observed in the skin

*Baez* In the external oblique muscle of the mouse and of the rat we have seen an architectural pattern similar to that which you have just described We were interested mostly in the presence or absence of muscular precapillary sphincters and their response to epinephrine or arterenol applied topically or injected intravenously I should like to ask whether or not you noticed in your studies a different set of reactions on the part of these vascular units in response to the different routes of administration?

*Zweifach* The evidence obtained by the direct observational approach indicates that epinephrine intravenously has a variable effect depend

ing on local tissue conditions We have observed an increased blood flow with low concentrations of epinephrine (1 μgm or less), a decreased blood flow with 2 0 μgm , and no effect with concentrations as high as 3 0 μgm in skeletal muscle after repeated contractions

*Green* I am still not clear about the communication between the artery and the vein on the surface of this muscle bundle Is it a capillary that runs longitudinally along this bundle also?

*Zweifach* These vessels are on the order of approximately 30 to 40 microns in diameter

*W Kinsely* Is this the largest size of the cross section of the vein, the band of 40 to 50 microns?

*Zweifach* The largest but least frequent type of interconnection was between vessels of about 50 microns, with the majority of interconnections ranging between 20 to 30 microns

*Green* What would be a conceivable function in muscle of such a large arteriovenous shunt? That would be a shunt and we can only think of shunts in terms of heat conductance, not as having any nutrient function

*Zweifach.* Our studies thus far have been restricted for the most part to descriptive morphology

*Nickerson* I think we can conceive of a function In no other tissue does the change from the resting to the active state cause such a marked change in oxygen requirement as it does in skeletal muscle It would seem to me conceivable that the shunts could represent a type of idling mechanism during periods of low oxygen requirement which could allow very rapid diversion of flow through the true capillaries within the muscle bundles when the oxygen requirement goes up Have you observed diversion of blood flow following stimulation of muscle?

*Zweifach* We do not have sufficient data to permit such a distinction

*Burton* May I sum this up? I would like to review the whole problem of the discrepancy and what is left to us First of all, blood flow measured plethysmographically is blood flow Clearance of radioactive sodium is some function of flow and the 'fudge' factor, $\theta$, which has something to do with diffusion That can be broken down into $\theta_1$ and $\theta_2$ if you like, $\theta_1$, as he suggested, concerned with the movement of the sodium up to the wall of the capillary, and $\theta_2$ something to do with the capillary pressure and the paths through which substances have to diffuse and have to filter through the vessel walls

If there is a discrepancy, then, it must be in this factor $(\theta_1 + \theta_2)$ I have thought about this for several years and puzzled over this discrepancy I very much favored the shunt as the explanation, that the total flow increased but it wasn't a "washing-out" flow Dr Zweifach's

observations would fit very nicely with the idea that maybe there is such a shunt But I changed my mind earlier in this discussion after hearing for the first time about the heat clearance as I like to call it the experiments which Dr Barcroft told us about Now I do not think a shunt is going to explain this because I cannot see why the clearance of heat the washing out of heat by the circulation should differ so much from the washing out of anything else by the circulation

If the explanation were a shunt flow it would seem to me that the heat should be washed out less quickly when the shunt was operating than when the flow is going to the capillaries Dr Stead raised the point that perhaps it was a change in the filtration pressures that mattered because the venous pressure in the small veins went up I thought that was fine, and a possible answer but then I remembered Pappenheimer s work (53) as Dr Kety did Pappenheimer quite definitely shows that in a peripheral capillary diffusion processes are so much faster than filtration that even if the filtration movement has gone in the opposite direction, the sodium will still diffuse and will hardly be affected Therefore, some factor of diffusion must be different for heat than for the sodium, and the only one I can think of is the final factor the passage through the pores which Dr Kety shows is normally not a limiting factor I think we are forced to an explanation in terms of some physical chemistry of the capillary wall I remind you that Pappenheimer found that the size of these pores is about 30 Å We must accept the fact that pores are there and their size can be very much affected, for instance by whether diffusion fluid is used with or without protein in it Adsorption of protein can very much change the filtration constant change it by a factor of ten times or so whether one uses a solution with or without protein

I am forced to an explanation of this discrepancy in terms of something that epinephrine does in a physical-chemical way I really feel now that I have heard about the heat clearance that I cannot use the shunt explanation any more

*Kety* Why not? A radiator can remove heat without having transfer of molecules across it

*Burton* Yes but suppose the shunt flow meant that the blood flow was not effectively washing the tissue Why should that not affect the clearance of heat? If heat flows through those tissues into the blood stream and if that blood circulation is changed to a shunt I would naturally expect that the removal of heat was decreased

*Kety* But the shunts that Dr Zweifach spoke of these very large vessels of 50 microns in diameter could very easily act as heat sinks

*Burton* Heat has to diffuse to it just as sodium

ing on local tissue conditions We have observed an increased blood flow with low concentrations of epinephrine (1 $\mu$gm or less), a decreased blood flow with 2 0 $\mu$gm , and no effect with concentrations as high as 3 0 $\mu$gm in skeletal muscle after repeated contractions

*Green.* I am still not clear about the communication between the artery and the vein on the surface of this muscle bundle Is it a capillary that runs longitudinally along this bundle also?

*Zweifach* These vessels are on the order of approximately 30 to 40 microns in diameter

*W Knisely:* Is this the largest size of the cross section of the vein, the band of 40 to 50 microns?

*Zweifach* The largest but least frequent type of interconnection was between vessels of about 50 microns, with the majority of interconnections ranging between 20 to 30 microns

*Green* What would be a conceivable function in muscle of such a large arteriovenous shunt? That would be a shunt and we can only think of shunts in terms of heat conductance, not as having any nutrient function

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*Stead* I don t either I always assumed this was right Dr Green do you know?

*Green* We made a few trials and did not get very good correlation with blood flow in skin and radio sodium uptake in skin

*Stead* I think if you can show it does occur in skin then you have a good point to back up this muscle theory

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*Kety.* It doesn't have to diffuse through actual transfer of molecules.

*Burton.* It does not make any difference. The law of diffusion is just the same. If the blood flow is further removed from the tissue, the heat is going to take longer to get from tissues to blood stream.

*Kety.* The sodium ion may not be able to get into the larger vessels whereas heat can. A steam radiator transfers heat without leaking steam.

*Burton.* That is my point, that it forces me to the final barrier of diffusion, the endothelial wall. There is the only place where there is a fundamental difference between the diffusion of heat and diffusion of sodium.

*M. Knisely.* And there you have a filtration pump working it out.

*Burton.* Again, you will recall that filtration pumping has very little effect on diffusion. Diffusion takes place at a rather fast rate compared to filtration.

*M. Knisely.* You are talking about fluid. I am not talking about fluid, I am talking about the sodium pump.

*Burton.* I had not thought of it as a pump which carried the sodium along with the heat.

*M. Knisely.* The movement of the animal itself.

*Nickerson.* This fits in nicely with the shunt idea. If the problem is simplified to a difference between sodium and heat with respect to $\Theta_2$, which is passage through the wall of the vessel, one of the major differences between the vessels that Dr. Zweifach has described as shunts and capillaries is in their walls. The walls of the larger vessels are thicker and include many elements besides endothelium. The additional tissue will markedly inhibit sodium passage, but it will have no more effect than an equal amount of fluid on the passage of heat.

*Burton.* I accept your correction in my thinking. I now think you are right!

*Nickerson.* This is simplified to the $\Theta_2$ factor, and it seems to me that the role of the $\Theta_2$ factor is best explained on the basis of shunts.

*Stead.* I think that this is relevant to the problem. Heating the skin, as I remember, increases the blood flow to the skin. Doesn't radioactive sodium, injected into the skin, also exhibit an increased rate of disappearance? This is the shunt mechanism par excellence, which is working well with the radio-sodium technic.

*Kety.* One group has shown an increase (48), another group (31) has not. But in any case you do not have a crucial experiment since the mere fact that you have an increase in shunt flow does not preclude an increase in capillary flow also.

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# THE CIRCULATION IN THE PERIPHERY

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THERE ARE THREE definitions of circulation in the periphery The first is the circulation of the blood through all the parts of the body except the heart chambers This definition has a great deal to recommend it because in shock the effects in one organ or the defenses against shock in that or another organ are affected by the general circulation or by neurogenic transmission The second is the circulation in a single tissue As has been well demonstrated here this definition has the great advantage that the regulation of the circulation in a single organ or a single tissue is a certain kind of regulation and it may be entirely different from the regulation of the circulation in another organ I have noticed however that the trend in this discussion has been toward a third definition of circulation in the periphery i e the blood flow in skin and in muscle Perhaps this third one is the best to consider and perhaps I have a little more to contribute in this than elsewhere

## TOTAL AND REGIONAL BLOOD VOLUMES

Thinking against the background of shock it occurred to me as it has occurred to you that a very important aspect of circulation in addition to the rate of circulation is the volume of blood distributed in one or another vascular bed or the volume distributable from one vascular bed to another Regional blood volumes must have important connotations in the general background which we are discussing

When I learned that Dr Bazett (1) had found that the total blood volumes of his subjects in summer were about 40 per cent higher than in the winter and that in 1922 Dr Joseph Barcroft (2) had found much the same condition in the case of normal subjects transferred from cool to hot environments the potentialities of shifts of such volumes interested me I began to wonder if this extra blood volume was mainly in the skin

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It is extremely difficult to measure the total vascular volume in skin, and I know of no satisfactory method, but if it is true that, during physiological conditions, 40 per cent of the blood volume can be lost or gained, and if it is in response to heat from the environment that it is gained, and to cold in the environment that it is lost, it would seem that the new volume that is gained in summer may be largely a cutaneous volume And then one is reminded that the shock level, the stimulus to produce shock, is frequently some 40 per cent of the blood volume lost, so it may be that the skin is a tremendous defense in shock because the best single indication that a patient is in shock is that the cutaneous circulation goes into vasoconstriction

In thinking of large potential volume changes, I was wondering what sort of changes in the vascular volume of muscle might take place They might be, at least early in the shock, in the opposite direction from those in skin I am reminded that Dr Henry Barcroft (3) made some fine studies which showed that in fainting and with decrease in blood volume from acute blood letting, the muscle flow increases, and I wondered if, along with the change in flow in muscle, there might not also be great volume changes I think there are no critical measurements, I wish you would supply them if there are

I have made slides which show the tremendous ranges of blood flow in the skin, and during this discussion Dr Barcroft has shown you the great changes in flow in muscle His work shows variations in muscle flow between 0 5 and 30 ml of blood per 100 ml of muscle per min As far as skin is concerned, various workers have shown that, in parts of the skin, flows may be as low as 1 ml per 100 ml per min and as high as 150 ml or more per min Granted these great differences in flow were in fingertips where there are rich arteriovenous connections to explain them, I wonder what we would find if we could study the flow of the total skin, especially of skin in response to a hot bath or to very hot weather

Bazett (1) quoted Benson (4) as reporting a 2 75 per cent increase in human limb volume resulting from immersion in hot (40° to 47° C) water That, in itself, is not a large figure, as he refers it to the cross section of the limb, but it is quite possible that the increase in volume was an increase in volume only of the skin, and if the figure is related to the volume of the skin, it is a very large factor

Up to this point I have purposely talked around this subject I think it is quite legitimate to speculate on the magnitude of changes in volume in individual vascular trees For instance, in the early picture of shock, with cutaneous vascular constriction, I wonder if the patient may not be receiving an excellent transfusion which is really quite effective in

reconstituting a reasonably good blood volume and if the enormous muscle vascular bed and volume might be competing with that and working in the wrong direction and if the spleen s emptying during this stage preceding shock may be only a small proportion of the transfusion which skin and muscle and other beds may be able to supply to the total central blood volume. I would like to ask if that is an impossible concept or whether it is worth some discussion

*W Kinsely* In what part of the world were these individuals in Bazett s study?

*Montgomery* Bazett (5) says the Boston difference is not as great His subjects were in Philadelphia and the studies were made in both winter and summer He admits that the 40 per cent is an extreme but he obtained it when he wanted it when the subjects were hot enough for a long enough time and cold enough for a long enough time He also quotes lower figures by W H Forbes (6) in Boston

Sir Joseph Barcroft s subjects were people who left a cooler country which I believe was England and went to a hotter place described as the tropics of the British Empire

*Baez* I should like to ask if there were any observations made of the extravascular fluid compartment at the time of the shifting of blood volume? What I have in mind is whether the 2 5 per cent volume change in the limb must necessarily all be in the vascular compartment May I also ask whether the body weights of the subjects studied showed any change?

*Montgomery* The weight changes according to Dr Bazett were negligible The so-called measurements of blood volume at that date were with dyes so his conclusion certainly was that this is intravascular blood volume change I do not think that his method was as good as the modern methods such as tagged red cells or tagged albumin

*Baez* The hydrostatic pressure must have been elevated in a given (skin) vascular compartment for quite a long time (4 to 5 days) and I am wondering whether all the extra fluid is kept intravascularly or whether the interstitial spaces and lymphatic vessels also participate in housing it

*Barton* A great deal of it has gone to veins While I was associated with Dr Bazett in this work years ago we took some really quite remarkable infrared photographs of the veins of the arm these photographs show that in 5 days of acclimatization to heat, great new veins appear and veins that I suppose have been there open up and the volume in the veins is very much increased So I think that Dr Bazett thought of this as in the circulation rather than elsewhere This is a change of volume in the circulation

*Nickerson.* What happens to the fluid when the intravascular volume decreases? Does it go into the cells, does it go into the extracellular space, or where does it go if the patient does not lose weight?

*Montgomery* It is a slow change as Bazett (5) described it In a hot environment there is an increase within a few hours of something like 10 per cent of volume which has not yet received its protein and red cells, but over the protracted period of something like 2 weeks in the hot environment there is a much larger shift in which the blood elements come up to the same counts for any one unit of blood as prior to that time I think that, as he described it, there was no large element of shift in total fluid into the tissues

*Burton* We studied the intake of food, water, and calories, and the output, and so on, but it is a very complicated matter and I do not have too much confidence in the results, however, the fluid balance calculated by that elaborate method definitely did change When the patients went into a hot place, their weights went up and so did the amounts of water in the body calculated by this method When they were in a cool place, their weights went down and, as I remember it, the changes in the weight were rather comparable to the changes in blood volume

*M Knisely* As I remember, Professor Joseph Barcroft boarded ship and as he approached the Equator he was astounded to find that the total red cell mass increased but as he went farther away from the Equator it decreased That was the beginning of the argument that led to the discovery of the spleen as a red cell reservoir

When he returned to England, he set up a closed room, the temperature of which could be raised or lowered His colleagues and he were able to duplicate, in this closed room, the changes in total measurable red cell amount which they had previously found by using the surface of the world for their heater and cooler This opens up a vast literature which I once covered to some degree in a monograph (7)

To return to the history, Stolnikow (8), Johansson and Tigerstedt (9) showed that the liver itself could store blood Using two dogs of comparable size, they took all the blood they could from one and transfused it into the other, the arterial pressure of the recipient did not rise When the recipient was opened, the liver was found to be swollen and very hard From this kind of experiment we know that the vascular system, particularly the liver of an animal, can accept and hold a tremendous amount of blood or of concentrated blood cells

The next step in the history showed that the liver or portal vein bed of man could store and release blood, as Krogh and Lindhard (10, 11, 12) have shown These investigators measured changes in their own cardiac output as they went from rest to work They found that the cardiac out-

put increased roughly from 4 to 21 liters per minute and what is most important they found that the increase in cardiac output began before there could be time for a recirculation of the blood From this Krogh deduced that the increase in cardiac output could only occur provided that in human beings there was a reservoir emptying blood into the circulatory system. And this reservoir would have to be just upstream from the heart Krogh deduced that the reservoir would have to be the liver and portal vein bed This was in 1912 After that Sir Joseph Barcroft and his colleagues (2 and 13 through 16) demonstrated that the spleen is a blood *cell* reservoir Many investigators have, since then shown that the spleens of other species including those of men can store concentrated red blood cells (17 through 36)

In 1915 Lamson (37) and Roca (38) demonstrated that the liver of dogs could store concentrated red blood cells This concept has been lost in the literature In our own laboratories using microscopes we have watched the sinusoids of spleen store concentrated red blood cells and we have also watched the sinusoids of liver store concentrated red blood cells Certainly all of the branches of the portal vein can dilate and thereby store enormous amounts of blood

Dr Montgomery raises the issue of the skin as a reservoir and this is extremely important because the skin is the largest single organ in the whole human body

*Gregg* Skin is the largest single organ? You are not including the muscle mass?

*M Knisely* I am not including the muscle mass The favorite of students is liver but it is really the skin.

*Gregg* But you are excluding muscle?

*M Knisely* I am excluding muscle mass The muscle mass in adult human beings runs from 20 to 40 per cent of body weight according to Vierordt s tables

*Bing* I do not think we should forget the heart because Hamilton (39) has shown a very marked change in the residual volume of the heart directly dependent on changes which you have described

*Stead* Dr Shorr we have here a lot of measurers of blood volume and I think we might find out whether or not we are dealing with an established fact—that volume does shift 40 per cent If it does I am willing to think about what it means and how it happens On the other hand if it does not I would rather forget about it until it is established one way or another Without asking for any discussion as to why they believe it I would like to start with Dr Bradley and ask the blood volume experts to tell us if we are dealing in reality or fiction

*Bradley* I am not quite sure what is meant by the term blood

volume" here As I understand it, Dr Burton states that there was a shift of blood into the veins and that the change in blood volume was, therefore, presumably a change in the circulating blood volume, not a change in the total blood volume

*Stead* Dr Montgomery indicated that was just like two beakers, one of which contained 40 per cent more than the other Isn't that the same as what you were saying—that when the blood volume increased and decreased things within the interior lining of the blood vessels changed 40 per cent?

*Montgomery* I was simply taking figures that are in the literature If they are correct I would wonder where the distribution is, because it seems to me that nobody has measured the shifts in volume in the organs having the great blood volumes, and it is important to know where the main volume changes might take place The skin is a very difficult organ in which to measure blood volume Please put me right if you know of a method

*Stead* But I am thinking of blood within blood vessels As I understand it, you mean 40 per cent of the blood left the vascular system, and that 40 per cent came back in Is this what you mean?

*Montgomery* No, I am saying that, if the measurements are correct, 40 per cent more blood by volume was present at one time than another under physiological conditions If so, where did it go? In a hot environment, why would it go anywhere but to the skin? If the vessels of the skin will hold that much blood, is the skin, then, a "reservoir" for either loss of blood or, as we see the shock condition clinically, a "reservoir" from which the body can be transfused?

With as large a muscle mass as there is and with the high flows possible in muscle, is the blood volume of the muscle vascular tree of sufficient size so that it, too, can act advantageously or disadvantageously in shock?

*Burton* It is of sufficient size that when it dilates further, a man bleeds into the muscle to such a degree that he faints This is well established by Barcroft and Swan (40)

Perhaps I can clear up the misunderstanding with the climatic experiments Presumably this was an increase in the amount of circulating fluid, not merely a shift All blood volume measurements merely measure circulating blood volume in the sense that they measure only the volume in which the dye, or whatever is used, is mixed, but in the first few days of acclimatization to heat or cold there is an immediate shift of the circulation in the body to the periphery The skin is flushed at once, but then in the course of 5 days there is not only this shift which has persisted, but also an increase in the total amount measured by the

conventional blood volume methods I would not want to argue whether or not the whole of this change might be due to some shift of what was circulating and what was in a backwater but no one can settle that question at present can he?

Dr Doupe (41) has made blood volume studies of very carefully controlled subjects These studies cover every month of the year and have been very consistent He finds a swing according to the seasons which amounts to approximately 25 or 30 per cent This is the first time this has been done so carefully and on the same subjects over so long a period

*Merriman* I do not think the change reported by Dr Doupe* was as much as 40 per cent

*Burton* No it was not 40 per cent it was approximately 20 per cent

*Nickerson* I think it was in the 20 per cent range, and the changes in blood volume appeared to be well correlated with the environmental temperature except that the spring increase in volume started somewhat before the temperature began to rise

I cannot answer for the human, but I can describe a few experiments on the dog This animal shows both acute and long term effects of a changed environmental temperature The acute effect, as seen by a change in blood specific gravity and in hematocrit may occur in fractions of an hour The long term change in blood volume which seems to require some weeks seems to be approximately 20 per cent Curiously enough, dogs tend also to show lower hematocrit and hemoglobin values (by about 10 per cent) in summer than in winter We have determined lethal bleeding volumes during all months of the year In winter these volumes are most consistent from animal to animal and show a relatively high value (4 5 to 5 5 per cent body weight) In summer the bleeding volume is more variable and lower (2 5 to 4 0 per cent) The higher room temperature in summer may have accounted for a large part of this difference But in spring and fall these volumes were more variable still ranging from a summer volume to a winter one and the room temperature in which the bleeding was done was not that variable But since man is not sheltered from environmental temperature by constant air conditions it seems that one must not conclude that simply because his blood volume may be high in summer his tolerance of blood loss would be correspondingly high

*Bradley* I wonder what the role of the splanchnic bed is in this situation We have been able to measure the volume of blood held in the splanchnic bed and we find in the dog that approximately 20 per cent

Doupe J Seasonal Variations in Plasma Volume Paper given at the Clinical Investigation Travel Club Winnipeg, October 21 1954

of the blood volume is contained there (42) With apresoline and hexamethonium bromide this volume can double so that approximately an additional 20 per cent of the circulating blood volume can shift into the splanchnic vasculature On the other hand, the splanchnic blood volume is greatly reduced following hemorrhage in dogs Thus the splanchnic vasculature contains a large amount of blood which may be sequestered, in a sense, outside of the active circulating mass However, this volume can apparently be mobilized under conditions of stress to benefit the systemic circuit and in other circumstances, certainly, can serve to pool or trap a portion of the circulating blood volume

*Bing.* But, Dr Bradley, would you not measure the amount that is trapped with the over-all method of blood volume determination? Is there actually any trapping which you could not measure with the dye?

*Bradley:* Yes, it may be impossible to measure volumes of blood into which the tracer material cannot penetrate You must remember that the technic we are using to measure the splanchnic blood volume (SBV) is based on a dilution of a circulating tag, and so is susceptible to the same difficulties that beset any method of blood volume determination In addition, less time is available for equilibration than in the method for measuring total volume It is conceivable that the value for total blood volume might include blood within the splanchnic bed which is not measured as SBV because enough time may elapse during the longer period of equilibration (usually 20 minutes in contrast to 2 or less) to permit penetration of the tracer

*Richards.* Can you obtain evidence of relative trapping?

*Bradley* I think we can An increment in circulating splanchnic blood volume when there is no change in total blood volume must mean that a larger portion of the blood in the body is held in the splanchnic vasculature I presume that it may be said to be "trapped" there

*W Knisely* In making blood volume determinations, what is the time interval between the introduction of the indicator and the reading of the indicator? In other words, what is the shortest length of time in which circulating blood volume could be measured?

*Bradley* I use the term "circulating blood volume" because I think this is the only volume in which rapid admixture of a tracer material can occur We administer $I^{131}$ labeled human serum albumin and remove blood continuously from the hepatic vein and a peripheral artery immediately thereafter The difference between the average concentrations in arterial and venous blood, between the time of injection and equilibration (i e , the time at which arterial and venous concentrations react equally), is the amount of tracer "trapped" in the splanchnic bed during equilibration per unit volume of flow during that time This

value multiplied by the hepatic blood flow per second and the equilibration time in seconds yields the total mass of radioactive material dispersed within the vascular bed at equilibrium Dividing this value by the equilibration concentration gives a value for the total volume of the bed Now the two concentrations come into equality in one minute or less It seems likely that dispersion by convection is very rapid in the circulating mass movement of the tracer thereafter by diffusion alone into sequestered blood should be so slow that the arteriovenous difference so produced is not detectable

*Gregg* If one is interested in total blood volume why doesn t one measure it in a period of standardized very light exercise rather than during a state of rest? I have never made a blood volume measurement under such circumstances but why couldn t it be made during exercise so as to take into consideration this volume of trapped blood that Dr Burton is talking about, if there is a volume of trapped blood that isn t in the circulating blood to which the dye goes?

*Stead* That has been done very extensively with red cell tagging and it does not change

*Gregg* Then there is not any volume of trapped blood

*Stead* Unless you give a reasonable period of time for it to mix in the normal person several minutes In sickness these factors come into play but these experiments are on normal people

*Burton* But unfortunately there are these disturbing factors which Dr Bradley would admit that in all the blood volume studies if volume is added to the circulating fluid by transfusion of 200 ml for example it is very rarely that 200 ml can be found in the blood volume determination Is this not true?

*Remington* Blood transfusions into unbled dogs cannot be accounted for quantitatively by red cell bookkeeping or by T 1824 dilution volumes A large portion of the transfusion is seemingly lost very promptly from the measurable circulating blood volume The loss of plasma and the loss of cells are not proportionate the former being larger

*Burton* There does seem to be some indication that added volume can go places that the dye or injection cannot reach

*M Knisely* Apparently this boils down to the problem of the specific nature and behavior of the anatomical devices which store whole blood or blood cells in the body In general our experience has been that blood and blood cells are stored in the spleen and liver This agrees with many very careful investigations of the past (7) In the spleen the red cells and in the liver the red cells or the whole blood are stored in sinusoids which are shaped roughly like sweet potatoes or cucumbers There are sphincters on each end of these sinusoids When

looking into a microscopic field, one can watch three or four sinusoids simultaneously Two *may be accepting and storing the blood*, there may be blood already stored in one Then each may change, one may retain the blood it has just stored and the sphincters of the other two sinusoids may open and allow blood to flow directly through There is often a continuous series of changes so that some sinusoids are storing whole blood or concentrated red cells while others are releasing them Thus, in every instance there is a certain amount of stored blood, but in any very short period of time some of this blood is emptied out and other blood is accepted and stored The sinusoids of the spleen store concentrated red cells only Liver sinusoids may store either concentrated red cells or whole blood Following a meal, the period during which any one set of blood cells is stored may be greatly prolonged In mouse spleen I have seen concentrated blood cells stored in a single sinusoid continuously for 10 hours The significant feature is that the durations of the storage periods are precisely integrated with the total physiology of the whole animal

*Montgomery* Do we know what happens to muscle?

*Zweifach* Dr Montgomery is referring to a situation which is chronic and in which there arises a progressive discrepancy between the available capacity of the circulatory bed and the volume of blood circulating through it As a consequence, there develops a gradual increase in the total blood volume to fill the increased vascular bed This readjustment apparently does not involve the shifting of blood from one area to another

Dr Remington raised the point that in summer dogs react poorly to stress in the form of hemorrhagic shock During the winter months, following the induction of hemorrhage, the skin circulation very quickly becomes ischemic and almost negligible During the summer months, in an animal which presumably has more blood available in the skin, the skin circulation does not react as effectively nor as completely The skin remains warm throughout the phase of compensatory vasoconstriction and there is no evidence to indicate that significant amounts of blood are being shifted away from the surface of the animal to the interior Apparently, in this case, we are dealing with the failure of a compensatory mechanism which is operative under winter conditions Thus, the presence of an increased blood volume in the skin during heat acclimatization may actually be detrimental to the compensatory activities of the animal, since this bed is no longer available for active redistribution of blood

*Montgomery* I was simply looking for potential sources of blood loss from, or of blood supply to, the central circulation, and I do not

think a single example i e the experiment on the dog in winter and in summer negates the idea that enormous shifts of blood can take place under extreme conditions if the volumes are there I only asked if it is true that the blood volume increases 40 per cent in summer where is that blood? I think it is in the skin If it is in the skin is it possible for the skin to hold 40 per cent of the blood volume? If the skin can hold 40 per cent of blood volume and under some circumstances (at least in man) can empty itself very completely doesn t that interest us as a source of blood and a source of loss of blood quite comparable to the spleen?

*Zweifach* I agree with you I would however like to emphasize the point that the presence of an increased circulating blood volume does not *per se* necessarily make an animal more resistant to a stress situation The basic consideration is the capacity to mobilize the circulating blood

*Burton* I would support that Dr Zweifach because Dr Bazett and I (43) found in these climatic experiments that, after the man had been acclimated to heat and had had this increase in blood volume cooling the room immediately caused the blood flow in the fingers to drop very markedly but, until the third day it did not drop to anything like the low level that it had before the subjects were acclimatized to heat. During the course of those 3 days there was a diuresis and approximately 1500 ml of extra fluid were eliminated from the body The vasoconstriction is not to the full level until this shift has taken place

This means that the climatic stress the stress of needing a peripheral vasoconstriction to keep in the heat is not sufficient to empty this reservoir Whether or not a hemorrhagic shock situation would be a greater stimulus and result in emptying this potential reservoir of the skin is a subject on which I know of no data

*Zweifach* Local factors within a particular tissue also influence the ability to redistribute the blood into other segments of the vascular tree A pertinent example of this situation is that which exists in skeletal muscle during stress Under normal conditions hemorrhage results in a profound vasoconstriction and a removal of this bed from the active circulation Following exercise the vascular bed in the same muscle will not vasoconstrict with hemorrhage despite the fact that the opposite limb muscle continues to undergo active vasoconstriction The vessels in the exercised limb remain open even at blood pressures as low as 40 mm Hg The capacity to respond to vasomotor stimuli can therefore be considerably modified by environmental conditions in that part

*M Kinsely* To return to the skin question for a moment Dr Leo

Massopoust of Marquette University has published a magnificent set of pictures showing changes in the diameters of veins in the body walls of women as they go into pregnancy There is an increase in the volume of blood in the skin of these women, at least in some areas of the skin

*Lamport* In the same direction, it seems to me that the use of the photoelectric plethysmograph, which includes in its reading the blood in the venules, might be helpful here in giving an integrated value for blood content, since you cannot see these venules in a gross photograph

*Cournand* I hesitate to introduce clinical material here, but there are two sets of observations which might be of interest in relation to some of the questions asked previously Firstly, at Bellevue Hospital a study was made of subjects suffering with traumatic shock and under the influence of alcohol These constituted about 20 to 30 per cent of the subjects under study at that hospital during the last war It was found that they were worse off with a lesser blood volume reduction than nonalcoholics and showed some tendency to have warm skin Sometimes they responded spectacularly to injection of vasoconstrictor drugs, this applies only to the group with a blood volume reduced by 20 to 40 per cent of the predicted value Secondly, with regard to the influence of circulation at various rates and through different parts of the body upon the direct measurement of total blood volume, cardiac failure would appear to be a test situation In the course of measurement of the total blood volume by the combined $P^{32}$ and T-1825 methods, Dr Alfred P Fishman and Dr Philip Samet in our laboratory have given vasopressor and vasodilator substances which act rapidly by the intravenous route in patients in cardiac failure They have been unable to detect any change in the alignment of the experimental points along the two slopes—that of the radioisotope count and that of the dye I think that man is different from the dog in that total blood volume measurement accounts only for a fast circulating vascular compartment

Finally, I would like to make a statement with reference to the type of shock that Dr Barcroft studied with O G Edholm and J McMichael, namely the vaso-vagal syndrome type, in which there is fast redistribution of blood It is difficult to compare this with other forms of shock, such as traumatic and hemorrhagic, because I doubt that a large volume of blood is held in the muscular mass of the upper part of the body in those types, since, in severe shock, pulsations disappear even in the large arteries of the arm, but they are still present in the lower limbs Although indirect evidence, this observation does not suggest that the blood volume can increase in the muscular mass of the upper part of the body

*Montgomery* I should think the fast flow to muscle almost certainly

fails in irreversible shock or just before irreversible shock Would it not Dr Barcroft?

*Barcroft* The observations that Dr Edholm and I (44) made were confined to the vaso-vagal syndrome Here we visualized that the loss of consciousness in some subjects was chiefly caused by an opening of the vessels in the muscles and a lowering of the peripheral resistance, offering to the blood a path of very low resistance from the arterial to the venous side and so depriving other organs of quantities of blood which would otherwise have gone through them

We have no observation as to whether the lowering of the resistance in the muscles did or did not mean that they contained more blood at a particular time

*Montgomery* You would hazard no guess as to the range of volume of the muscular vascular bed?

*Barcroft* In the vaso-vagal syndrome I am sure there was a big decrease to the resistance to flow in the muscles but I do not know about the volume in the muscles

I would like to say another word in connection with Dr Cournand s interesting point about the force of pulsation I think it is difficult to judge from a feeling of the force of pulsation what the situation is in regard to the blood flow We were very impressed in studying these vaso-vagal syndromes by the fact that it was not possible either to feel the heart beat or in some cases even to hear the heart beat with the stethoscope over the apex the reason presumably being that resistance to flow in the periphery was so low that the force of the heart beat was too small to be detectable on the surface by such methods

*Cournand* I was speaking of peripheral pulsations the femoral pulse was always discernible

*Barcroft* When my father went on the Royal Society expedition on the S S Victoria for the purpose of studying the effect of high altitude in the Andes (2) the members of the expedition took measurements of the blood volume by the carbon monoxide method at very frequent intervals and as Dr Knisely said they found that the blood volume increased until they got through the Panama Canal to the Equator then, as they went down the coast of South America it decreased again They felt that they had not obtained a proper basis for studying the effect of altitude on blood volume because they did not know really what their blood volumes were

If I recollect the order of change there was something like a liter in the total of 5 liters which would be about a 20 per cent change in the blood volume and then when they got back to England Fetter and Davies (45) repeated observations of the blood volume raising the

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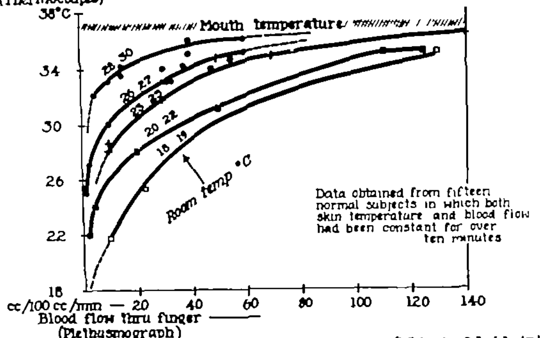



FIGURE 22 Relationship of digital skin temperature to blood flow through the adjacent finger at various room temperatures Reprinted by permission from Montgomery H Naide M. and Freeman, N E. Significance of diagnostic tests in study of peripheral vascular disease *Am Heart J* 21 *780 (1941)*

would pertain to data obtained by the thermoelectric needle method that Dr Barcroft has mentioned

*Burton* Except that the muscle is sometimes hotter than the deep body temperature

*Montgomery* We have seen this principle backward We have obtained estimates of blood flow in a hot water (43 C) environment by finding that the skin temperatures during the slowest flows approach the temperature of the water and those of the fastest flows approach the lower temperature of the body I suppose it is through a curved line but we do not have sufficient data on that

*Nickerson* What room temperature is this related to?

*Montgomery* A temperature of 22°C

## TISSUE OXYGEN TENSION

You probably remember that many years ago chemists were using an electrical method to estimate various concentrations of certain chemicals in solutions using the so-called polarographic method If one through a suitable circuit an example of which is shown in Figure 24 puts a suitable electrode in a suitable solution and increases the voltage the

temperature in the chamber, because my father thought perhaps this was a temperature effect, and within 48 hours they found an increase of about a liter also

*M. Knisely* The experiments were very carefully controlled They even measured the coefficient of expansion of the frameworks for the devices that measured gas volumes I was delighted that they checked up on that

*Montgomery* The figure quoted by Bazett (1) from your father's work was 38 per cent, but that may have been an extreme, and I was taking extremes to make the point, since it is quite conceivable that under shock conditions extremes could exist

## RELATION OF SKIN TEMPERATURE TO BLOOD FLOW

*Montgomery* I would like to discuss briefly the relationship of skin temperature to blood flow in skin This is apropos of the heat-flow relationships that Drs Burton, Kety, Lamport, and others discussed previously Their remarks concerned muscle, however, these data concern skin, not muscle Some years ago, Dr Burton made plethysmographic measurements while I made other observations and we published the data separately (Figure 22) At various room temperatures from 18° to 30°C we took air-plethysmographic measurements of flow in the tips of normal fingers, the distal half of the finger, and simultaneously took skin temperature measurements of adjacent fingers, and the relationship was found not to be a straight line The relationship of skin temperature to flow turned out to be, from the rather scattered data, a nest of curves, each curve appropriate for a single room temperature, lowest flows approaching room temperature, and the highest approaching body temperature, as one would expect

More recently in our laboratory D Felder and E Russ made another study, with the air-plethysmograph, of flow in the tips of normal toes, at a room temperature of 20 5 ± 2°C They made simultaneous measurements of skin temperature on the same toe-tips As you know, there are great variations in flows spontaneously, especially in fingertips Each of the points in this graph is an average of a number of skin temperatures and of digital flows during a 6-minute period, a period that was chosen because, during it, and for 6 minutes preceding and for 6 minutes thereafter, skin temperature was stable (± 0 5°C) The lag of skin temperature after blood flow change was in this way minimized

So here again as flow increases, as temperature increases up toward body temperature, the curve swings up asymptotically toward a horizontal a little below body temperature I suppose the same sort of thing would necessarily hold, would it not, to some extent for muscle and it

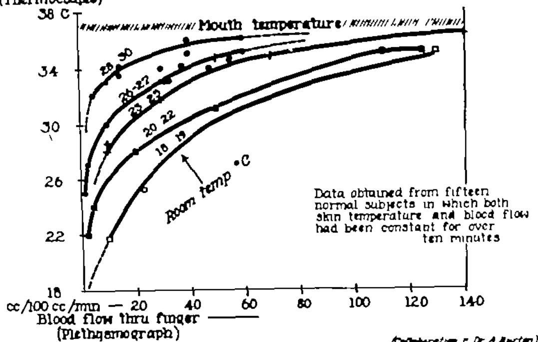



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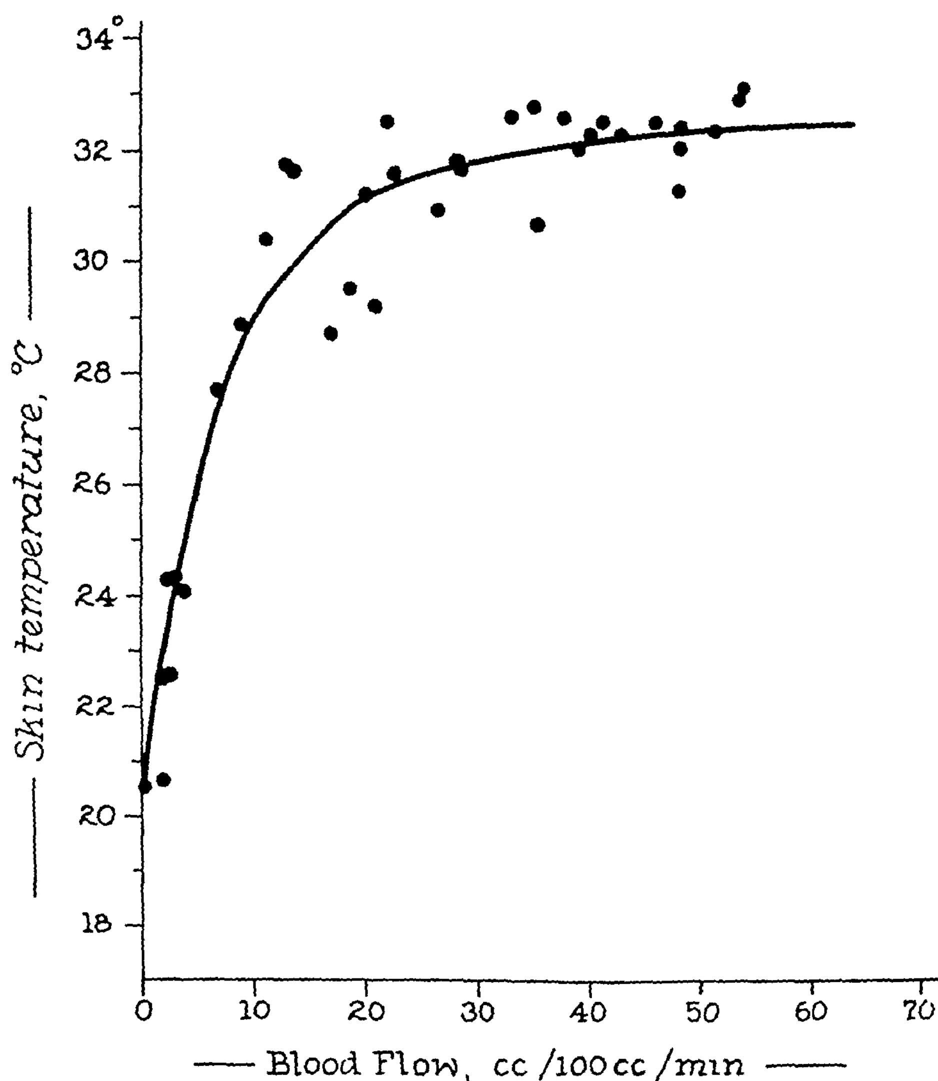



FIGURE 23 Relationship between skin surface temperature and measured blood flow in toe tip at room temperature 20 5 ± 2°C Plethysmograms were taken only when skin temperature was constant Each point is the mean of three to seven flow measurements All data from February 13, 1952 to July 17, 1952 are presented Reprinted, by permission, from Felder, D , Russ, E , Montgomery, H , and Horwitz, O Relationship in the toe of skin surface temperature to mean blood flow measured with a plethysmograph *Clin Sc* 13, *251 (1954)*

current which flows has some sort of relationship to the voltage A characteristic curve is obtained such as is shown in Figure 24 In other words, there is a certain current for a certain voltage when the electrode is in a certain concentration of a certain solution, and there is a plateau of current over a short range of the voltage

In Dr Detley Bronk's laboratory at the University of Pennsylvania, Dr Davies and Dr Brink (46) took a platinum electrode (cathode) with a suitable circuit, used the electrode in solutions in which various

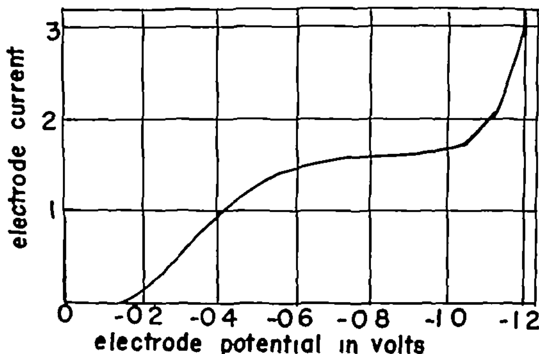



FIGURE 24 Current voltage curve for electrode in air saturated saline When a very small negative voltage is applied to a metallic electrode in a solution containing dissolved oxygen, there is a reduction of the oxygen at the electrode surface resulting in a small flow of current through the electrode. With increasing voltage, rate of reduction and resulting current increase until a voltage in the neighborhood of —0 6 volt is reached At this voltage the oxygen is reduced as quickly as it reaches the electrode surface Further increases in voltage have little or no effect on current until a voltage is reached where reduction of hydrogen ions commences

concentrates of oxygen were present and at an emf of approximately 0 6 volt they found a straight line relationship between the concentration of the oxygen and of the current that flows They applied this principle to the study of oxygen in solutions bathing living nerves and then they measured oxygen tension on the surface of the cat s brain

Dr M G Larrabee and Dr R Hodes* used such an electrode in the skin of the forearm and did two things They breathed pure oxygen and found that the electrical current increased considerably and they inflated a blood pressure cuff on the upper part of the arm above arterial pressure and found marked decreases in the current

Dr Orville Horwitz and I (47) saw this and thought it might be a useful tool in the study of peripheral vascular physiology and disease Figure 25*a* shows a cathode which is illustrated in more detail in Figure 29 There is an indifferent electrode *b* with calomel half-cell *g* or silver

* Unpublished data

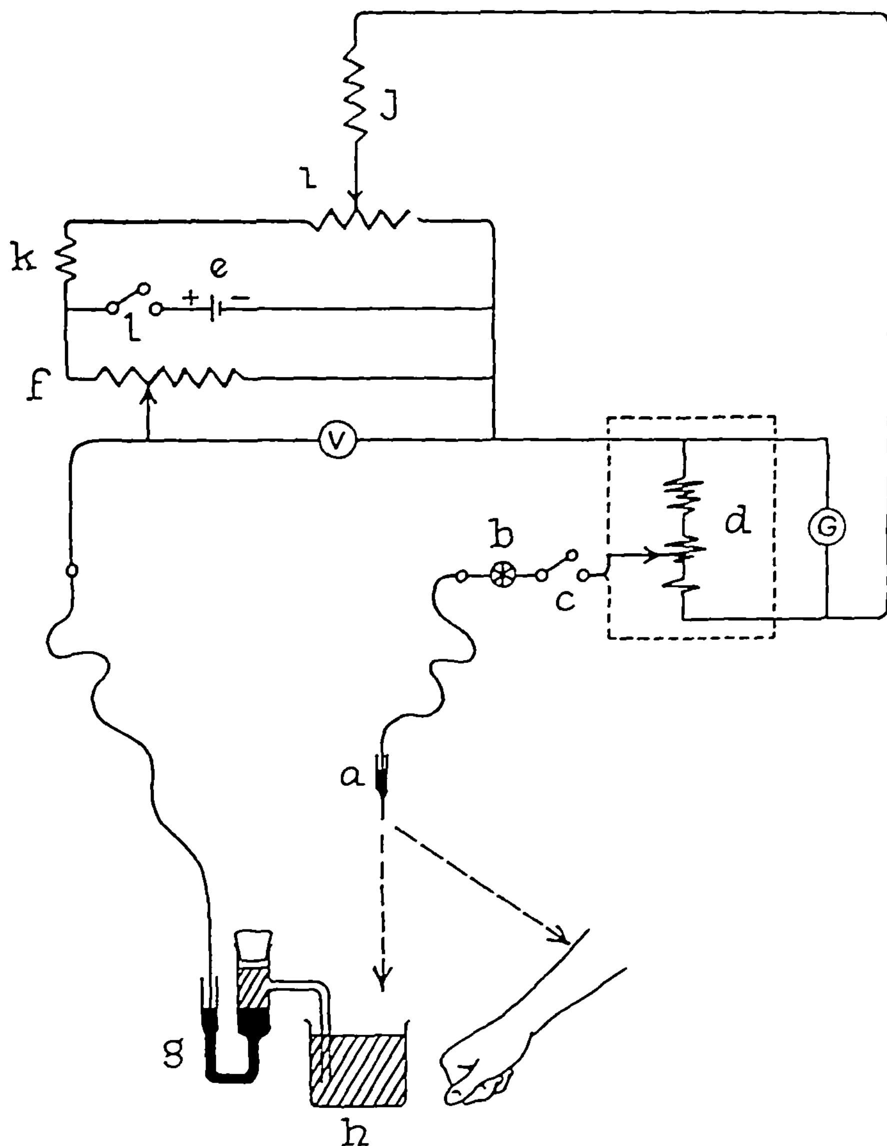



FIGURE 25 Wiring diagram of circuit for polarographic determination of oxygen tension *a* electrode tip (cathode), *b* selector switch (controlling six electrodes), *c* electrode switch, *d* Ayrton Shunt (Rubicon No 1243) (resistance 0 to 65,000 ohms), *e* dry cell (1 5 volts), *f* variable resistance (500 ohms), *g* calomel half-cell (anode), containing 0 9 per cent NaCl, *h* 0 9 per cent NaCl in beaker, *i* variable resistance (10,000 ohms), *j* fixed resistance (2,000,000 ohms), *k* fixed resistance (40,000 ohms), *l* main switch, *G* galvanometer (Rubicon No 3418), *V* voltmeter Reprinted, by permission, from Montgomery, H , and Horwitz, O Oxygen tension of tissues by the polarographic method, introduction, oxygen tension and blood flow of the skin of human extremities *J Clin Investigation* 29, *1120 (1950)*

silver chloride cell in which a finger can be placed and a sensitive electrode (cathode) having a diameter of a 26-gage needle, can be placed in

skin Subsequently Mr George Peirce made studies of muscle possible by designing other electrodes

Figure 26 shows the electrode as it might appear in skin. A platinum wire protrudes through a glass tip and is brought to a point by sharpening on a stone some mercury makes contact between the platinum and the circuit, and perhaps the skin looks something like this It was soon apparent that, if we took such an electrode and calibrated it in a solution of known concentration of oxygen and then made a measurement with it in skin that had a fast blood supply and presumably because of that fast blood supply a high oxygen tension, we did not find the oxygen tension that one must expect in such skin.

What we are really measuring is the rate of diffusion of oxygen to the tip of the electrode the tip of the electrode is constantly reducing the oxygen so that there is a big diffusion factor that differs in a solution and in a tissue

We then took some excised human skin, inserted an electrode in it and put it in physiological saline having a known oxygen tension We at first obtained zero current zero oxygen tension The reading remained zero for nearly an hour and then the current slowly rose and came to a level I then realized that the skin must at first have been alive and using oxygen and then it had died and become passive to the oxygen in the surrounding fluid

We then used freshly dead skin as a means of roughly calibrating such electrodes for use in skin and reported oxygen tension in mm Hg in some of the work

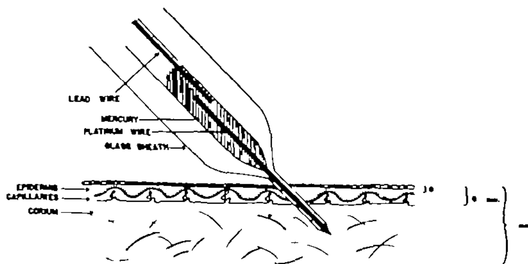



FIGURE 26 The open type platinum electrode of Davies and Brink, for determination of oxygen tension

Figure 27 shows a small apparatus that will do the major part of this work without any recording

Figure 28 shows another apparatus, an electronic one, that permits

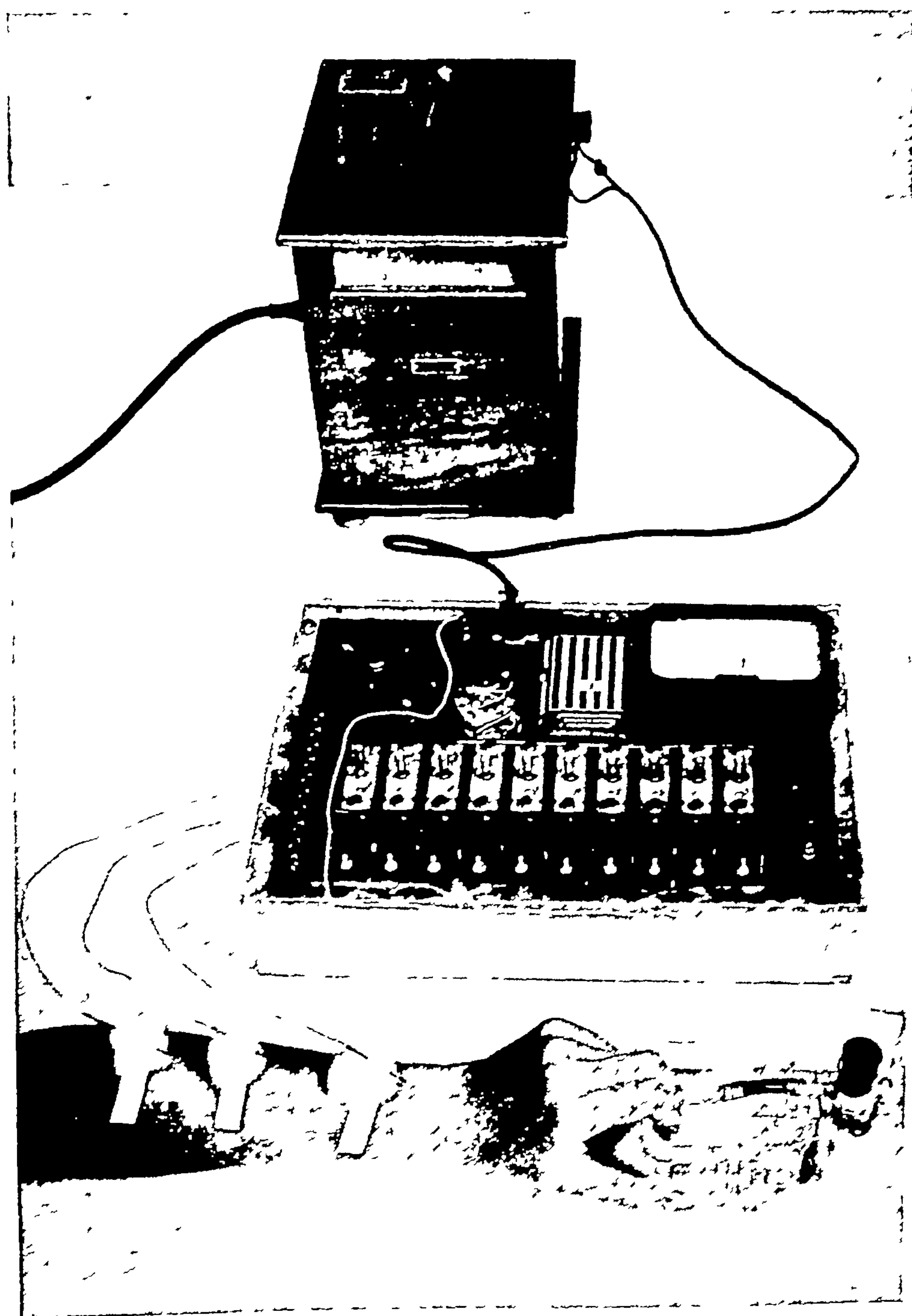


FIGURE 27 Usual apparatus for determination of oxygen tension—three electrodes in the skin of forearm

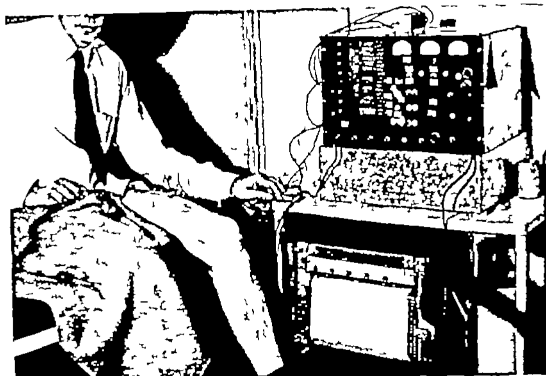


FIGURE 28 Electronic apparatus for polarographic determination and recording of oxygen tension

automatic recording and also measures smaller oxygen tensions It is used here in following changes in oxygen tension in thigh muscles

Early in the work we made known solutions of oxygen and recorded the current flowing through electrodes in the solutions and through electrodes in dead skin in the solutions (Figure 29) Readings were made after 10-second closures of the circuit We obtained a linear relationship between the current (in galvanometer units) and the known oxygen tension The upper line *A* shows experimental results in the known solutions The lower one *B* was obtained in the freshly dead skin equilibrated in known solutions that is for a known oxygen tension there was a slower diffusion rate to the tip of the electrode in skin than in the solution but the relationship was not changed from a straight line

*Nickerson* May I ask if in this calibration on skin, you are assuming that the diffusion of oxygen to the electrode through the dead skin is comparable to diffusion from the capillary bed to the electrode?

*Montgomery* That is right but we may in time find need of corrections

*Nickerson* Are not your distances quite different?

*Montgomery* They may be but we have evidence that they are not

Figure 27 shows a small apparatus that will do the major part of this work without any recording

Figure 28 shows another apparatus, an electronic one, that permits

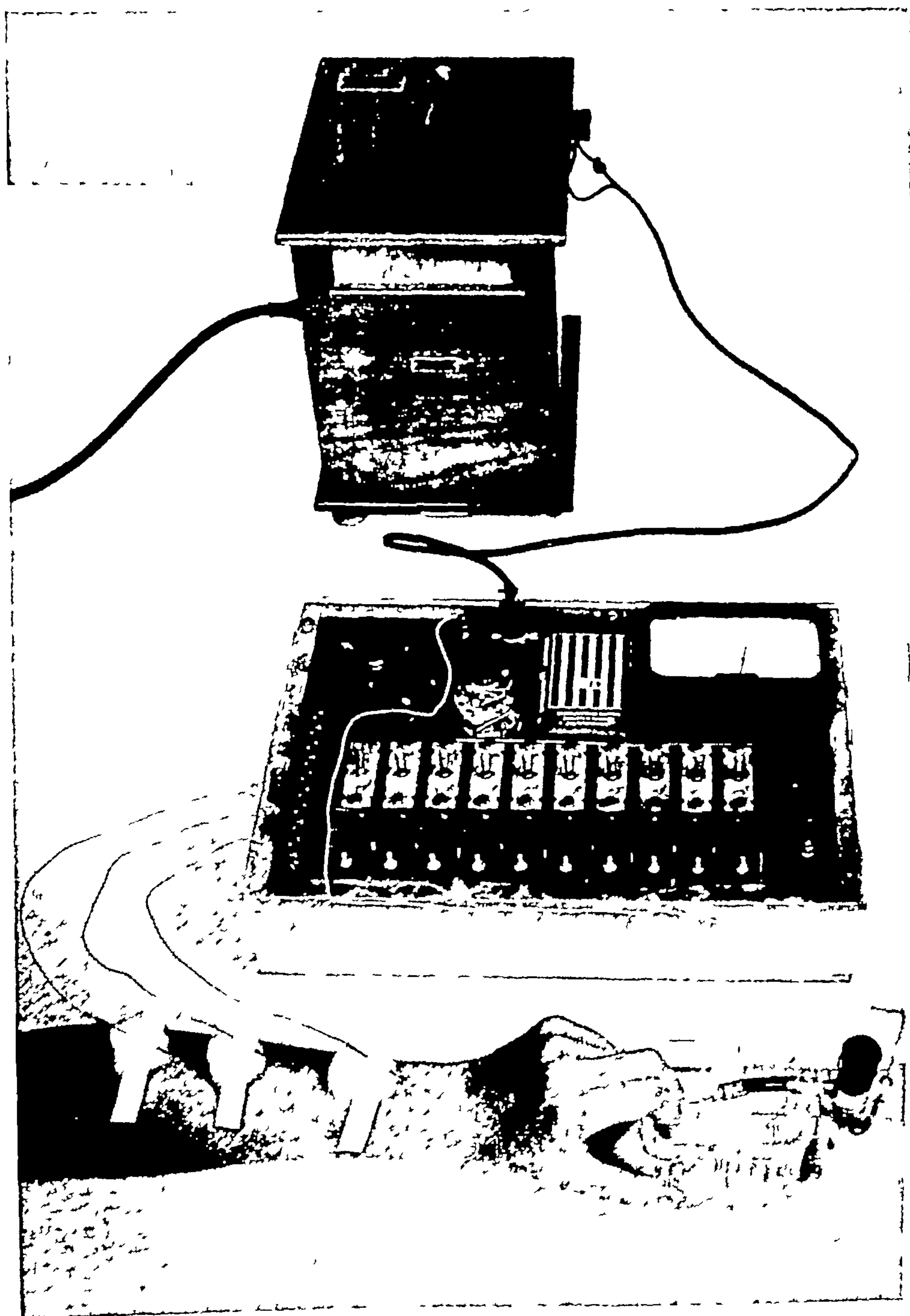


FIGURE 27 Usual apparatus for determination of oxygen tension—three electrodes in the skin of forearm

a very slow circulation We think this method will emerge as a useful method of study of oxygen tension in various tissues

In studying oxygen tensions of solutions it soon became apparent that there was an important corrective factor for different temperatures and that this factor is approximately that of the influence of temperature upon gaseous diffusion. Figure 30 is obtained from our experimental data and can be used to correct oxygen tension to a single temperature The same correction applies to a tissue as to a solution

We used the rough calibrations in dead skin in trying to obtain a quantitative measure of the oxygen tension in live skin The example shown in Figure 31 is from intact skin of a normal toe during vasodilation When oxygen was breathed as it was twice during this experiment, there were great increases in skin oxygen tension An open mask was used When the blood supply was made negligible by a pressure

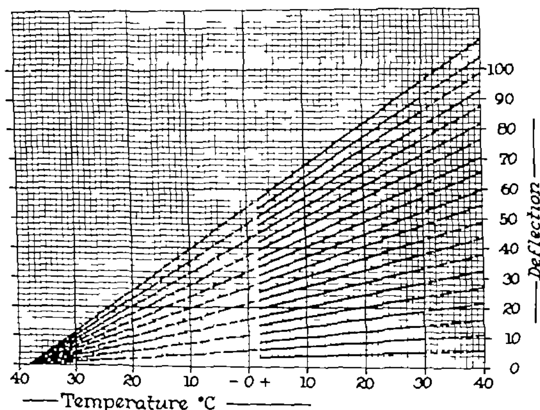



FIGURE 30 Temperature correction chart To correct a galvanometric deflection taken at one temperature *a* to the deflection expected at another temperature *b* at the same oxygen tension locate *a* and follow along nearest line drawn through the vanishing point of all lines, and read *b* Reprinted by permission, from Montgomery H and Horwitz, O Oxygen tension of tissues by the polarographic method introduction oxygen tension and blood flow of the skin of human extremities *J Clin Investigation 29 1120 (1950)*

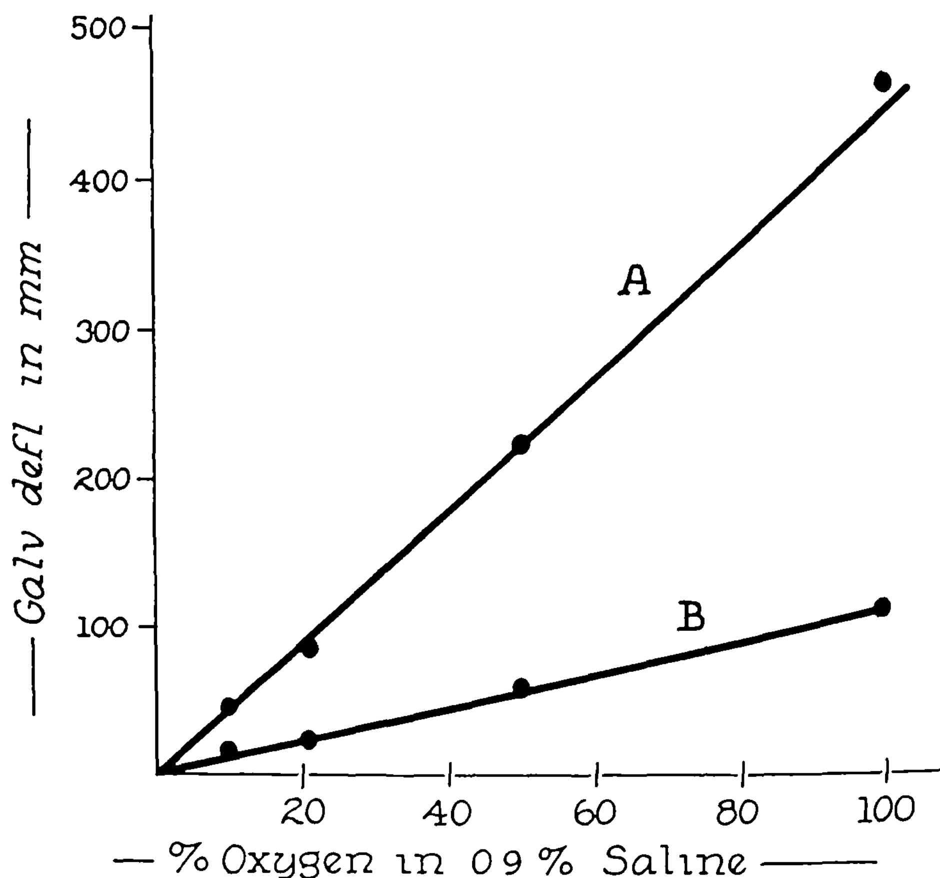



FIGURE 29 Current-oxygen tension relationship simultaneous measurements of current from *A* electrode tip (electrode No 4) in 0 9 per cent NaCl and from *B* electrode tip (electrode No 6) in excised, dead skin in 0 9 per cent NaCl Curves show effects upon current of various known tensions of oxygen in the saline Correlation coefficient of points along *A* is 0 99, along *B* is 0 98 These characteristic differences in slope are only slightly influenced by the differences in the two electrodes Temp 23 5° ± 1°C

severely so It is certainly not a live, functioning skin, but it is the nearest thing to live skin that we can get that does not consume oxygen

*Nickerson* There are no areas in skin that are as far as from a capillary loop as the distance from the solution to the center of the dead skin

*Montgomery* The electrode is large relative to capillaries, and touches many capillaries, and there is evidence that the diffusion distances are not greatly changed by changes in circulation I hope we can shortly have some discussion of this, although it may sound a little like the discussion we had earlier, concerning the rate of disappearance of radioactive sodium However, in a later Figure, I shall show that we did obtain expected values for oxygen tension in living skin having a fast blood flow and greatly decreased oxygen tensions in skin having

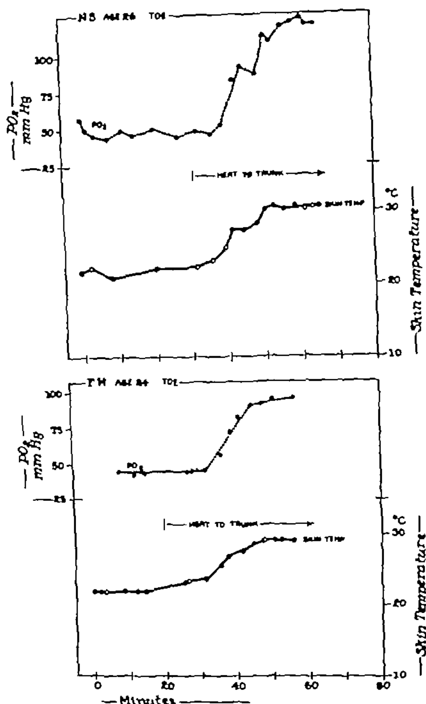



FIGURE 32 Effect of physiological variations in blood flow upon oxygen tension of skin of toe of two normal female subjects Electrode No 6 (for its calibration characteristics see Table XI on page 149 Blood flow through skin of toe was increased reflexly by heating pads on the body Room temperature 23 C.

We made a number of oxygen tension measurements in the skin of toes using this calibration of the oxygen tension With intact skin when the cutaneous vessels were gently vasodilated we obtained an

cuff on the thigh, the oxygen tension slowly decreased to zero, and returned when the cuff was deflated There were many such measurements This is an average one and I think not in any way a picked one

In the experiments illustrated in Figure 32, simultaneous measurements were made of oxygen tension and of temperature of skin of toes Room temperature was constant at about 23°C Heat was applied to the body and caused reflex vasodilation in the toes Oxygen tension is plotted here in mm of Hg, starting in this instance (upper graph) at about 50 mm and going to some 125 mm The skin temperature values of the toe and the corresponding blood flows are shown In other words, as there was a rise in blood flow in the skin, there was a rise in oxygen tension The cutaneous oxygen tension increased to about the expected value for plasma equilibrated against air The results are of the expected order of magnitude Many experiments were made subsequently to learn more about the changes of oxygen tension in skin that result from changing blood flow

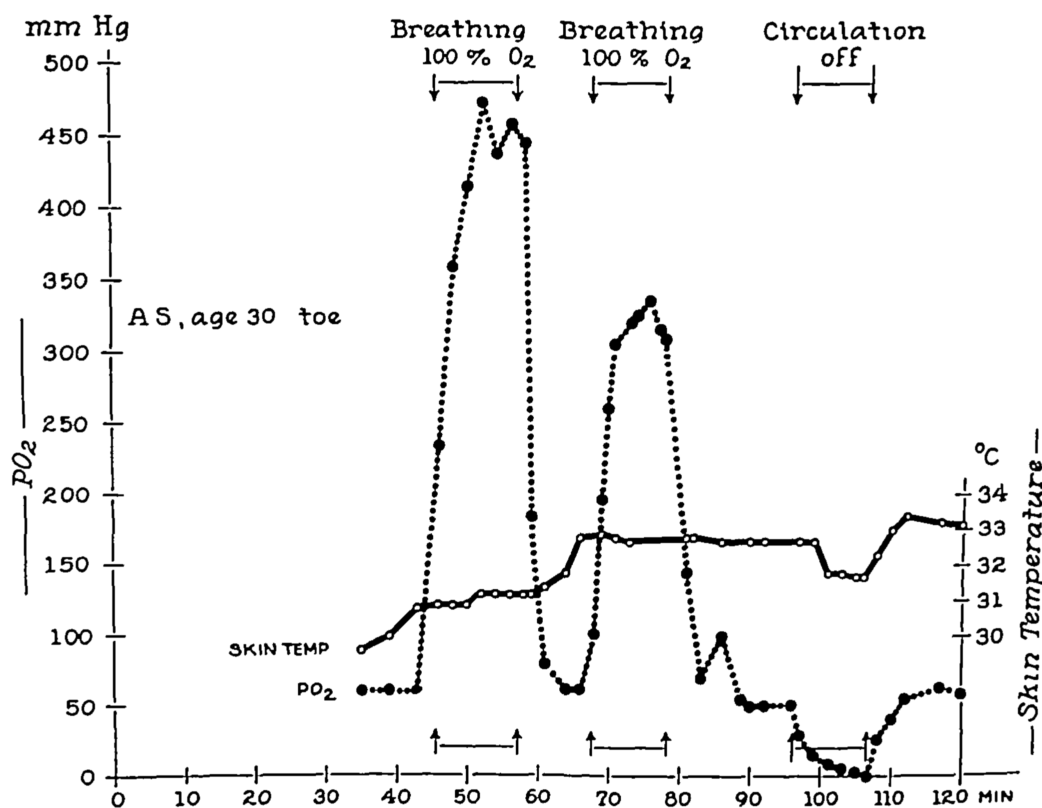



FIGURE 31 Effects of oxygen inhalation and of arrest of circulation on oxygen tension of skin of toe of a normal female Oxygen given by open mask at rate of 15 liters per minute Circulation arrested by blood pressure cuff on lower leg, with pressure 50 mm Hg above systolic Room temp 25 5°C

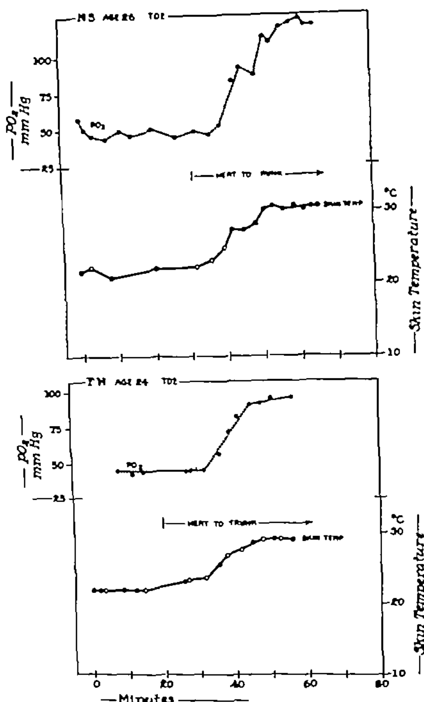



FIGURE 32 Effect of physiological variations in blood flow upon oxygen tension of skin of toe of two normal female subjects Electrode No 6 (for its calibration characteristics see Table XI on page 149 Blood flow through skin of toe was increased reflexly by heating pads on the body Room temperature 23 C.

We made a number of oxygen tension measurements in the skin of toes using this calibration of the oxygen tension With intact skin when the cutaneous vessels were gently vasodilated, we obtained an

average value of 87 mm Hg The measurements in the same skin during vasoconstriction averaged 28 mm Hg The measurements in toes having severe peripheral arterial occlusive disease, when the limbs were in vasodilation, averaged about 18 mm Hg, and the skin of these same toes during vasoconstriction had even lower values We now know that in normal subjects when there is severe vasoconstriction, the oxygen tension may be even smaller than any of the figures just cited Blood flow is then extremely slow

I suppose it is fair to say that arterial blood in the normal subject has a value *circa* 100 mm Hg pressure and that with infinite blood flow we should obtain a mean value of 100 mm in skin Skin has a low metabolism, and, on occasion, a very rapid flow, so we should approximate arterial values from measurements in vasodilated skin

Figure 33 shows another way to demonstrate the great variation of delivery of oxygen to a tissue (the skin in this instance) over extremes of vasodilation and vasoconstriction A number of measurements were made by Dr Raymond Penneys (48) of the time taken for increments of oxygen, furnished by the lungs, to appear at the electrode tip in the skin of extremities in various degrees of cutaneous vasodilation and vasoconstriction The top curve is the change in per cent saturation of warm ear blood as measured by the oximeter, and is much the same for all experiments on any one subject The time of arrival of oxygen in the skin of the extremities varies widely, depending on the peripheral vascular tone In the case of a normal person in marked reflex vasoconstriction ("cool skin," 25°C), we found the first increment in oxygen in the skin to occur in 90 seconds When, however, the extremity was lying in hot (45°C) water and the body was kept warm, oxygen arrived in the skin of the extremity several seconds after being detected in the ear by the oximeter, showing the tremendous range of blood flow in the skin

Since our average value for vasodilated skin was not far different from that expected for arterial blood, Dr Penneys (49) made a study to relate oxygen saturation (oximeter reading) to oxygen tension in the vasodilated skin, and made a sort of "*in vivo* dissociation curve" (Figure 34) He labeled the reading of initial tension as 100 per cent, varied the oxygen content of the inspired gas to as low a level as was safely feasible, and from many experiments drew the curve shown The rate of change of slope fits the conventional dissociation curve of human blood almost exactly Though it is not safe to try for lower figures, the result further substantiates the use of the oxygen electrode in warm skin to obtain approximate values of arterial oxygen tension

Even in warm skin we do not know for certain that we are measuring

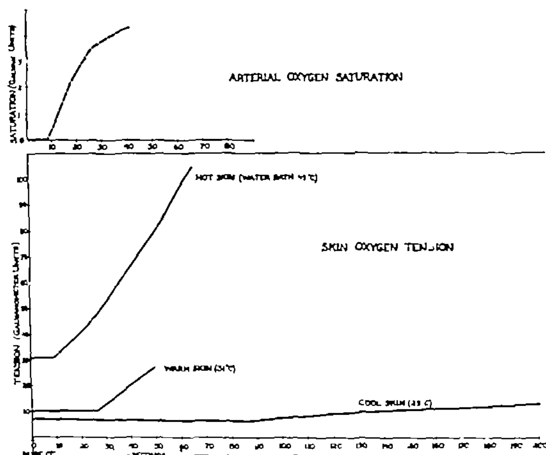



FIGURE 33 The first change in the arterial oxygen saturation of the blood and in the oxygen tension of warm, cool and hot skin—three typical experiments on three different subjects Saturation changes are essentially the same in all experiments $O_2$ indicates beginning of inhalation of oxygen Reprinted by permission, from Penneys, R and Montgomery H Oxygen tension of tissues by the polarographic method the rate of movement of oxygen from the peripheral artery to the skin *J Clin Investigation* 31 *1042 (1952)*

solely oxygen tension However in solutions wide changes in pH and salinity appear to have no effect

We do know that we can put the instrument to practical use in various ways one of which is the following Dr Harry F Zinsser Jr Dr Horwitz, and I (50) found the electrode as useful as measurements of samples of arterial blood, in detecting right to-left shunts It is much less disturbing to the patient than is the conventional method employing arterial blood sampling On breathing oxygen through a B and B mask the skin oxygen tension of patients without right to-left shunts increases on the average of 314 per cent that of patients with right to-left shunts by 29 per cent The lowest of the first group was 100 per cent the highest of the second 45 per cent, so there was a clear distinction

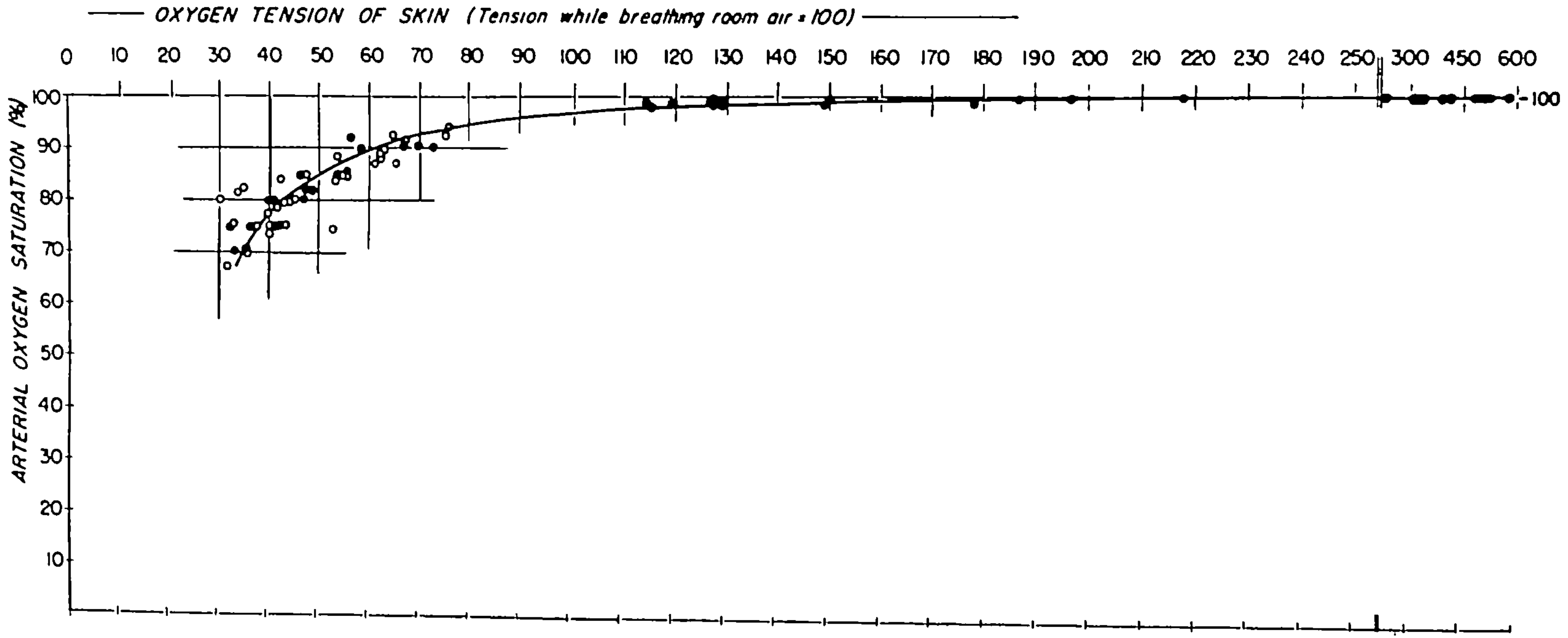



FIGURE 34 Relationship of oxygen tension of skin to arterial oxygen saturation (oximeter) in warm (vasodilated) skin Reprinted, by permission, from Penneys, R Oxygen tension of tissues by the polarographic method, skin oxygen tension vs arterial oxygen saturation, relationship to oxyhemoglobin dissociation curve *J Clin Investigation* 31, 204 (1952)

between the two groups with nothing even approaching an overlap In other words the method can be used to advantage in rough estimates of arterial oxygen tension since only a very small proportion of the oxygen of fast flowing blood is extracted by skin Indeed in the case of tensions approximately 200 to 500 mm obtained by breathing high oxygen mixtures the method seems to compare very favorably with the conventional *in vitro* methods

Dr Horwitz (51) used the electrode to explore the problem of optimum environmental (air) temperature for normal and ischemic limbs (Figure 35) He put electrodes in the skin of the legs gradually increased the temperature of the air around the legs and measured the changes in temperature and in oxygen tension in the skin of the legs Oxygen tension increased with skin (surface) temperature in normal subjects up to skin temperatures of 43 ± 2 C and in the ischemic legs up to 41 ± 1 C. With further increases in skin temperatures oxygen tension decreased and pain developed During the heating there must be an increase in blood flow an increase in dissociation of oxygen from the warmed hemoglobin and therefore, in the supply of blood and oxygen to the tissue and an increase in metabolism of the skin At 40

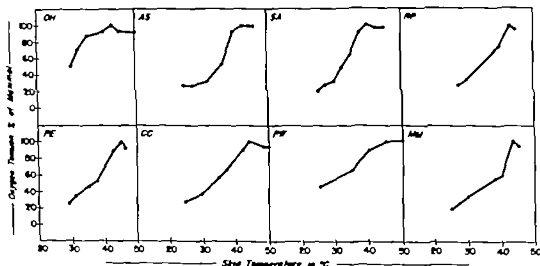



FIGURE 35 Effect of changing air temperature upon the cutaneous temperature and oxygen tension. Illustrating relationship between oxygen tension and surface temperature of the skin of normal extremities in eight subjects Oxygen tension readings are expressed on a relative rather than on an absolute basis with 100 representing the maximum value obtained by any one electrode Each determination was corrected for the physical effect of temperature upon the electrode reading Skin temperatures below 20 C are not graphed here Reprinted, by permission, from Horwitz, O Peirce, G and Montgomery H. Oxygen tension of tissues by the polarographic method the effect of local heat on the oxygen tension of the skin of extremities *Circulation* 4 111 (1951)

to 44° C, maximum oxygen tension results Oxygen utilization then outruns the increasing supply of oxygen by reason of limits of increasing flow and dissociation and a continued rise in oxygen utilization That is probably the correct explanation One could not say that this is the clinically optimal temperature of a limb because it is not oxygen alone that is needed in the ischemic extremities I offer it as an example of the use of the electrode in clinical investigation

I think if we become involved in a prolonged discussion of this, we will encounter many of the same factors that Dr Kety did earlier There are gradients around the tip of the electrode There are probably differences in rate of diffusion in different tissues, or differences between that in solutions which can flow and in tissues that cannot flow

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# MESENTERIC LYMPHATIC DYNAMICS IN THE RAT*

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IN THE LITERATURE, extensive studies on the flow of lymph may be found (1), but there is less information specifically concerning the flow in the intestinal (lacteal) lymphatics That the mesenteric lymphatics in rats and guinea pigs aid in the movement of lymph by contracting was recorded by Heller in 1869 (2) These early observations were overlooked for a long time Nearly 50 years later several investigators (3, 4, 5), independently of each other, and apparently without knowing of Heller's work, fully confirmed his observations Florey (6) extended the observations to other mammals, including man, and concluded that lacteal motion is characteristic only of the rat and guinea pig A detailed explanation for the active lymph flow in this group of mammals, however, is lacking

The demonstration of mesenteric lymphatic contraction and lymph flow by means of motion pictures is not new (7, 8) It has been postulated (7) (*a*) that the flow of lymph in the lacteals is mainly effected by segmental contraction of the lymph vessels (a segment being that portion of a lymph vessel between two valves), denying the existence of waves of contraction resembling peristalsis and (*b*) that the action of the valves in preventing regurgitation is passive and dependent entirely upon the force of the reverse flow In the course of our observations of the terminal vascular bed in the rat mesentery, we became aware of a different, constant pattern of dynamics in the lymphatic vessels, namely (*a*) lymph flow occurs without segmental contraction of the vessel wall, (*b*) waves of peristaltic movement are present, (*c*) valves appear to be active organelles which open and close rhythmically without the need for the force of a back flow This does not exclude the presence of segmental wall contraction and passive valve closure

*Aided by a research grant from the National Institutes of Health, U S Public Health Service (Grant H-79)

Examples of our observations may be seen in Figures 36 37 38 extracted from a motion picture of the mesentery of the normal fed rat An Eastman Kodak Special Camera with a Zirconium arc lamp was used for cinemicrographic recording at a speed of 24 frames per second *

*Burton* I would like to ask what evidence you have of independent contractility of the valves How can you be sure this is not a passive opening and closing caused by changes in pressure brought about by peristalsis?

*Baez* The motion picture demonstrates this point clearly A wave of peristalsis along the wall of the lymph vessel will certainly close the valves (Figure 36*B*) however between the peristaltic cycles vigorous and spontaneous closing and opening of the valves take place (Figure 37 *A* and *B*) and this occurs in the absence of reversal of the lymph flow

*Burton* I was wondering how you could be sure unless you can see all of the wall back to the next valve that there is not a difference in the pressure on the two sides which is causing that valve to move

*Baez* With the low power of the binocular microscope (x40) one can have in the field as many as four to eight segments of the lymph vessel The number to be seen varies from one preparation to another In the lymphatics of the normal rat mesentery the following three features may be observed

1) *Wall motion* (*a*) Waves of peristaltic movement run along the entire length of the lymph vessels They can be visualized best by moving either the microscope or the separate 3 way pinion stage so as to follow the fast progression of a given wave of peristalsis from its initiation at the central end of the vessel otherwise with the field fixed this rapid movement appears as a total instantaneous constriction of the wall (Figure 36*B*) (*b*) Partial segmental wall contractions occur anywhere along the wall between two valves but most often in the vicinity of a valve or at the confluence of tributary vessels

2) *Valve motion* (systole and diastole of Florey) In order of frequency valve closing and opening occur as a result of (*a*) spontaneous action, independent of both peristaltic waves and partial wall contractions (Figures 37 38) (*b*) an advancing peristaltic movement which always closes the valves on its course or (*c*) partial mural contraction occurring in front of a valve This may or may not close it apparently depending on the momentum of the intrinsic forces which control the valve motion

* At the symposium this film was presented. For publication Dr Baez has chosen illustrative frames from the film.




FIGURE 36 Portion of two lymphatic segments demonstrating A normal resting state of wall and valve showing rich vascularity about the valve site, *B* the same two lymphatic segments in a state of over-all contraction in the wake of a peristaltic wave which closed the valve x40 Not retouched

3) *Lymph flow* (*a*) Lymph or chyle can be observed flowing rapidly, independent of any distortion of the wall from its normal resting state (*b*) Peristaltic waves and partial wall contractions aid its progression




FIGURE 37 Two stages of a lymph valve in action *A* Open *B* Closed in the absence of either a peristaltic wave of contraction or back flow Note the unchanged diameter of the lymph vessel wall (x320) Water immersion Not retouched

toward the mesenteric lymph nodes and thoracic duct (*c*) Back flow occurs when a strong segmental partial wall contraction occurs at a moment when the distal valve is tightly closed and the proximal valve is in

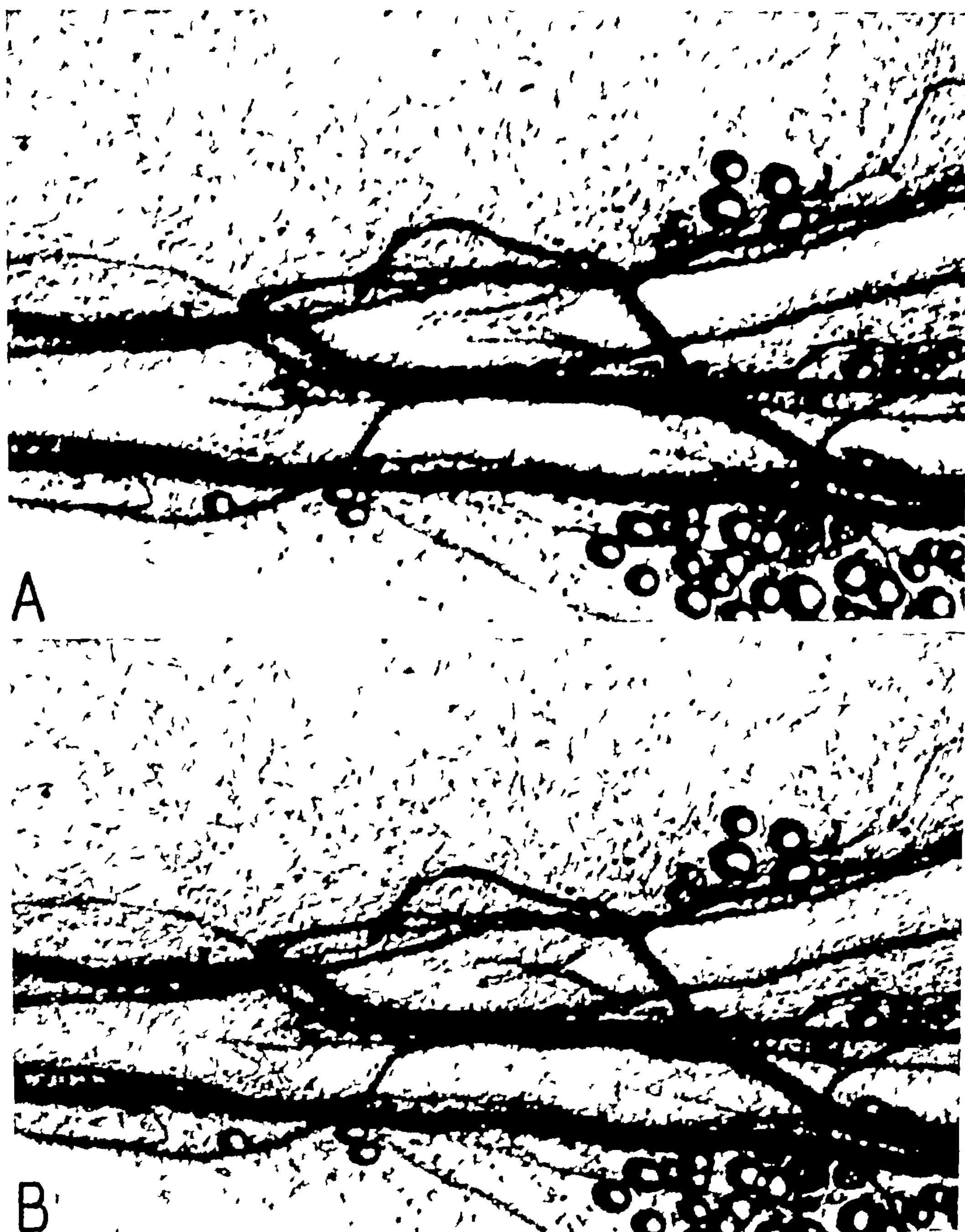



FIGURE 38 *A* Two intermediary lymph channels are shown on the right and the origin of a collecting lymph channel on the left, also three valves in diastole *B* The same vessels as above, showing independent closing (systole) of the valve in the upper channel, with the two valves in the lower channel remaining open x40 Not retouched

mid-diastole The gush of retrograde flow does not go very far as it is detained by the first closed valve

*Nickerson* Are you interpreting the pressure relationships in front of and behind the valve on the basis of the movement of particulate matter in the lymph stream?

*Baez.* In order to maintain as normal a preparation as possible for these studies no extraneous material was injected The flow of lymph can readily be observed and occasional leukocytes are always present to aid as guides

*Nickerson* The particles which were probably lymphocytes went both ways As a matter of fact retrograde flow seemed to be quite com mon

*Baez* Yes retrograde flow does occur The motion picture shows very clearly one of the points of our contention namely that the valves behave as active organelles They remain open despite a strong rush ing backflow

*Lamport* Have you ever encountered a situation where the wall of the lymph vessel was damaged and opened so that you presumably would have no change in the intralymphatic pressure because of leak age? In such a circumstance did you still see the motion of the valve?

*Baez* That is correct In fact the situation can be induced experimen tally at will, with dissecting microneedles Furthermore several seg ments of the lacteals can be dissected and will keep contracting for in our experience as long as 30 to 40 minutes

*Lamport* In the motion picture you indicated that you administered epinephrine What do you mean by the same dose of epinephrine is it given intravenously?

*Baez* By the same dose we mean that in this particular experiment we applied topically a total amount of 0 01 μgm of epinephrine in 0 2 ml and for comparative study we injected intravenously the same amount of the drug 0 01 μgm in a volume of 0 2 ml

*Lamport* Using the intravenous injection causes a tremendous dilu tion.

*Baez* That is true Both the intravenous dose and the topically ap plied epinephrine are undoubtedly diluted The final effective concen tration, at the target structures under observation, is so inconceivably dilute as to be out of the realm of my imagination

*Zweifach* With the method of topical application of epinephrine it is difficult to be certain of the concentration of the drug which actually reaches the target vessel When a comparison is made between the ef fective concentration of epinephrine as determined by surface applica tion with that which is effective by direct injection into the tissue with a micropipet the order of magnitude is about 1000 1

*W Knisely* Was it necessary to control the diet of the rats? Did you

reduce the fat intake? The reason I ask is that there is very little fat present in the mesentery, and this has been a problem to me in trying to observe this sort of thing

*Baez:* These were normal rats, maintained in their cages up to the time of administration of the anesthetic agent (sodium pentobarbital 35 mg/kg I M ) on their usual laboratory diet (Wayne Laboratory Blox "F") and tap water *ad lib* I presume you must have used rather large rats for your observations The latter have excessive amounts of fat in the mesentery along the blood and lymph vessels, however, in rats weighing from 100 to 150 grams we have always found good sites, consisting of fat-free lymphatic channels

*Lamport:* How do you explain the fact that the topical solution acted differently from the intravenous injection?

*Baez* I should like to review the difference in the reactions of the blood and lymph vessels to the stimuli of topical or intravenous administration of epinephrine and arterenol When either of these agents was applied topically in the field of observation in a concentration of 0 01 μgm , a distinct slowing down of the blood flow was noticeable within 15 to 25 seconds, while nothing altered in the lymph vessels A narrowing of the muscular metarterioles and a closure of precapillary sphincters could be observed (when these structures were present in the observation field) On the other hand, when an equivalent amount of either of these agents was given intravenously in the same preparation, the lymph vessels exhibited a marked enhancement of vasomotion, the number of constrictions per unit of time was increased as well as their intensity No response was discernible in the accompanying blood vessels The lymph vessel response occurred within 25 to 50 seconds after the intravenous injection, lasted 2 to 3 minutes, and then came back to its normal rate of six to twelve constrictions per minute

At present our data do not permit an exact explanation for this difference in the responses to topical and intravenous administration However, I should like to point out that when a stronger concentration of epinephrine or arterenol (1 to 2 μgm ) was injected intravenously, both systems of vessels responded In this case, the blood vessels responded immediately, while the time lapse for the response of the lymph vessels was 20 to 40 seconds This latter observation suggests that perhaps the stimulation of the lymph vessels may be indirect, the ultimate agent being other than the injected one But at present this is only an assumption

*Zweifach* In most studies of peripheral circulatory hemodynamics, little or no mention is made of the terminal lymphatics The assumption has been made that these represent a static system of vessels With

hemorrhage or traumatic shock the terminal lymphatics in the intestinal mesentery or in the mesorchium undergo profound contractions They show a form of vasomotion which is enormously exaggerated The sensitivity of these lymphatics to vasoactive agents is sufficiently high to permit their use as a bio-assay index It is apparent that the lymphatic vessels possess a dynamic physiology concerning which there is no direct information

M *Knisely* There is another very important factor in which the changes in the volume of tissue spaces of muscles and changes in the amount of fluid in the lymphatics coming from muscles must be taken into account The major blood reservoir of the body is the liver and portal vein bed The spleen stores and releases concentrated red blood cells

It is almost certain that the blood and blood cell reservoirs respond by emptying out controlled amounts of their contents not only to changes in the capacity of the various vascular beds of the body but also to changes in the capacity of tissue spaces and lymphatics When a small amount of fluid passes out of the vascular system let us say into connective tissue spaces either the vascular system must contract down to fit the remaining liquid or else the blood reservoir must contract and thereby inject some liquid into the circulating blood When a striated muscle goes from rest into a rhythmically working phase a great many capillaries in the muscle open up thus the blood capacity of the muscle is greatly increased (9) For a time after the muscle begins to contract rhythmically the blood flowing through the newly opened capillaries loses a considerable amount of fluid through the capillary wall into the tissue spaces (These capillary walls have not previously had a blood supply for some time and must be presumed to be quite hypoxic at this time) As the muscle continues to work rhythmically and the blood continues to flow through capillaries these newly opened capillaries which at first lost fluid out through their walls cease losing it (10)

The phenomenon to which I would like to call your attention now is that the blood volume reservoirs respond not only to changes in the volume of the various peripheral vascular beds but also to changes in the capacity of the tissue space and lymphatics It is my opinion which goes beyond the possibility of presenting the detailed evidence that the blood and blood cell reservoirs continuously respond to the algebraic summations of the capacities of peripheral vascular beds tissue spaces and lymphatics It certainly is not safe to think only of the possible changes of the blood and blood cell reservoirs as responses to peripheral vascular bed capacity changes alone

I would agree completely with Dr Zweifach that the tissue space and lymphatic capacities, and their variations, must be included in order to think accurately about this whole series of phenomena

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# THE CIRCULATION IN THE SPLANCHNIC AREA

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## COMPARISON OF BLOOD FLOW AND OXYGEN CONSUMPTION

SINCE HOMEOSTASIS of the splanchnic circulation is such a broad subject, I have chosen only two facets of the problem for discussion The first is the relationship of the splanchnic flow to splanchnic metabolism as measured by splanchnic oxygen consumption

The data used were taken from human subjects unless otherwise indicated and the flows were estimated by Dr Bradley s BSP (bromsulphalein) technic which in the absence of marked liver damage gives very reliable estimates of splanchnic blood flow however the estimates should be taken with some reservation when liver damage is more extensive Another point is that these are comparisons of splanchnic flow with splanchnic oxygen consumption, which means oxygen consumption in the liver together with its associated portal viscera since we have no means of measuring portal venous oxygen values in a living subject

Let us consider some of the simpler relationships first (Figure 39) Plotting these three groups of individuals together gives in general an exponential curve so that in all three groups the product of the flow and the A V (arteriovenous) oxygen difference gives a constant splanchnic oxygen consumption For example in the individuals with heart failure, as flow goes considerably down, A V oxygen difference goes up in a fully compensatory fashion and the reverse situation is true in the anemic individuals (1 2) In the persons with heart failure there is considerable splanchnic vasoconstriction, since arterial blood pressure was not significantly changed in this group

A comparison of these data with Figure 40 which shows the more common data contrasting cardiac output with mixed A V oxygen difference gives the same sort of curve but with a little more consistency

Figure 41 shows that a very similar situation also occurs when dogs are bled (3) There is the same sort of curve as before However in

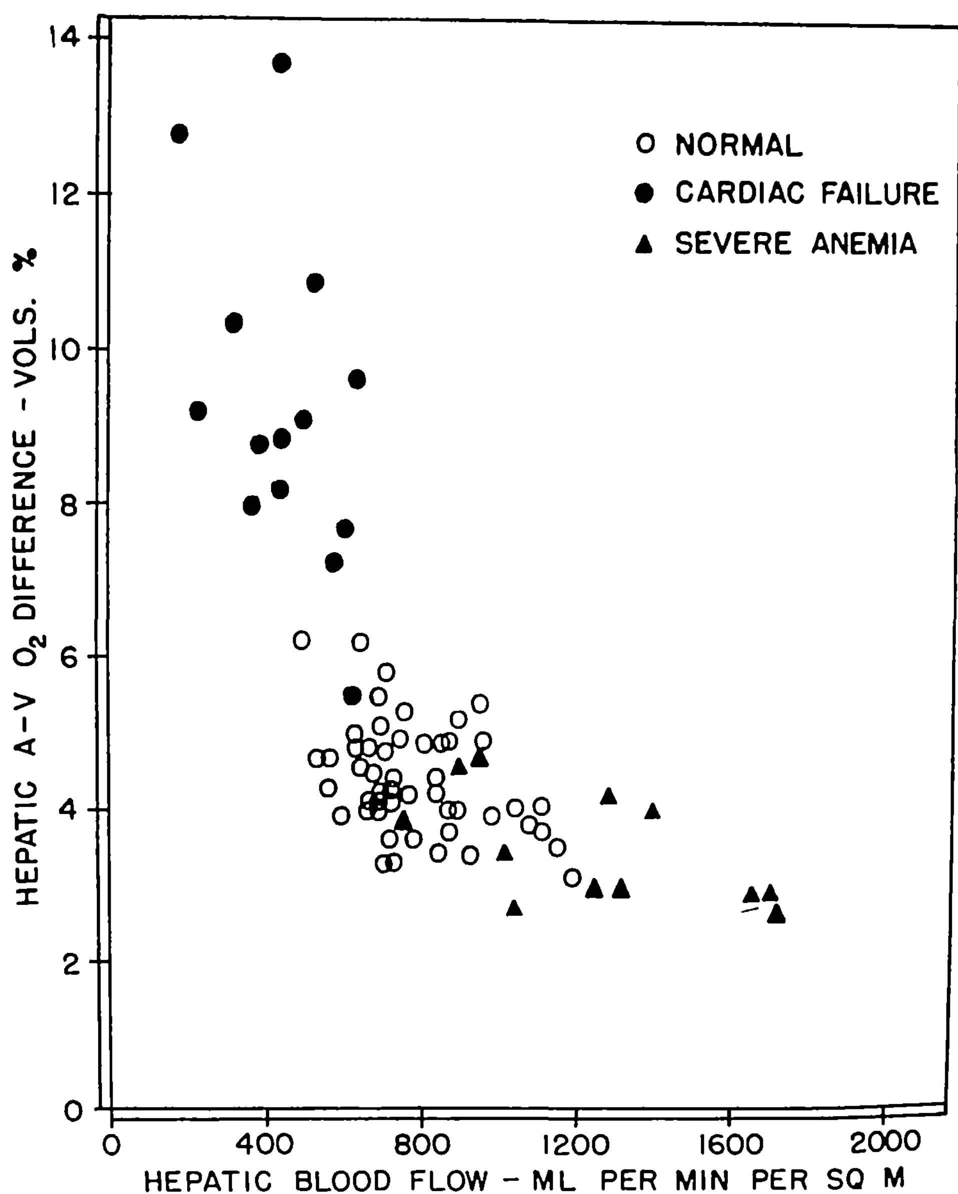



FIGURE 39 Hepatic blood flow and arterial-hepatic venous oxygen difference in normal control human subjects (open circles), in patients with congestive heart failure (closed circles), and in patients with severe anemia, i.e., less than 7 gm of hemoglobin (triangles).

this figure the association between the individual open dots and the corresponding closed dots is not clear, but Table IV provides the mean data for this group of thirteen dogs. It is evident that the flow decreased very strikingly and significantly, and the A-V oxygen difference rose in a fully compensatory fashion, so that the splanchnic oxygen consumption was maintained at exactly the same level before and after hemorrhage.

*Shorr* How much of a hemorrhage was there?

*Myers* This was a hemorrhage that was fairly sizable, i.e., from 32

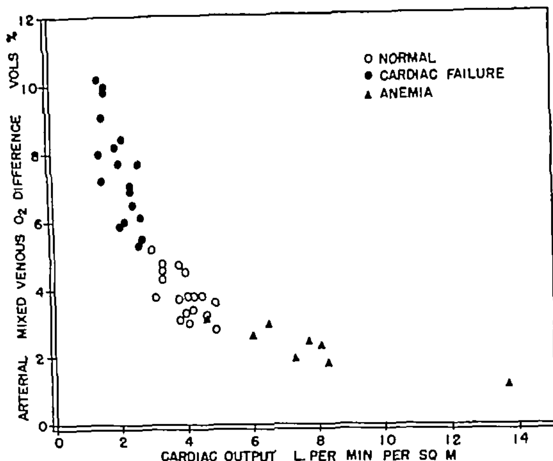



FIGURE 40 Cardiac index and mixed A V oxygen difference in normal control subjects (open circles) in patients with congestive heart failure (closed circles) and in patients with severe anemia (triangles)

to 65 per cent of the estimated blood volume It usually brought the mean arterial blood pressure down to levels of 60 or 70 mm Hg during the period of measurement and then there was some restoration with time

*Shorr* To about what level?

*Myers* In general to about 70 to 90 mm Hg These results are very similar to those found by Sherlock in human subjects who have fainted here again there was a marked drop in flow and a compensatory increase in A V oxygen difference These then, are the fairly simple circumstances in which the system compensates for a decrease in flow

Figure 42 shows what happens with a more severe hemorrhage, again in a dog The animal is bled into a Lamson bottle the arterial pressure being stabilized at 40 mm Hg Here there is a marked fall in total oxygen consumption (the solid line) and a very striking decrease in splanchnic oxygen consumption This condition has gone beyond the compensatory powers of the animal s system

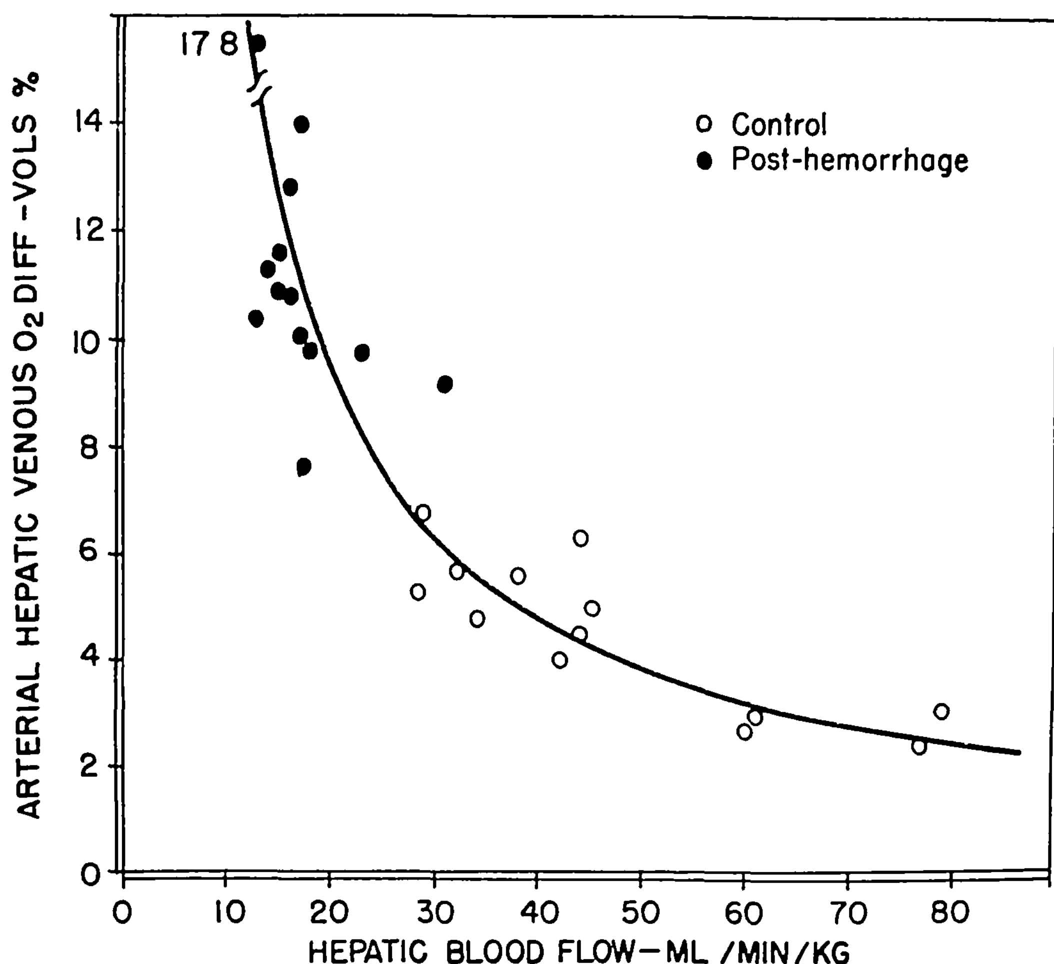



FIGURE 41 Hepatic blood flow contrasted with arterial-hepatic venous oxygen difference in dogs undergoing a single hemorrhage of from 32 to 65 per cent of the estimated blood volume Reprinted, by permission, from Hamrick, L W, Jr, and Myers, J D The effect of hemorrhage on hepatic blood flow and splanchnic oxygen consumption of the dog *Circul Res* 3, 65 (1955)

The fact that the ratio between splanchnic and total oxygen consumptions is the same before and after hemorrhage is not to be taken with any great seriousness That was more or less a coincidence in this particular experiment In most others, the ratio of splanchnic oxygen consumption to the total was higher after the bleeding than it was before, but this was not a consistent pattern

*Cournand* Have you studied shock in dogs which were already anemic?

*Myers* No, we have not, but in some of these dogs we gave sizable amounts of dextran, which of course diluted the hemoglobin and made the animals anemic, and in those instances they did *not* recover well from their state of shock

*Cournand* I asked the question because in studying human subjects

## TABLE IV

**Mean Data on Hepatic Blood Flow and Splanchnic Oxygen Consumption in Dogs Before and After a Single Hemorrhage of from 32 to 65 Per Cent of the Estimated Blood Volume (Series of 13 Dogs)**

| | Control | Hemorrhage | p Value |
|---|---|---|---|
| EHBF Ml/min/kg | 17 ± 1 8* | 18 ± 1 1 | <0 01 |
| Hepatic A V O Difference Volumes % | 1 6 ± 0 1 | 11 3 ± 0 7 | <0 01 |
| Splanchnic O Consumption Ml/min/kg | 1 9 ± 0 1 | 1 9 ± 0 1 | >0 5 |

*Standard Error

suffering from shock the only time we have observed a very striking reduction in oxygen consumption was on the occasion of a large gastrointestinal hemorrhage which occurred in patients who were chronically anemic from repeated gastrointestinal bleeding In other words the severe hemorrhage occurred in a subject with already considerable hemodilution

*Myers* Of course if the subject becomes significantly anemic the A V consumption cannot be increased enough to help In the dextran treated dogs which were anemic there was no possibility of their restoring their oxygen consumption in this general area barring tremendous increases in splanchnic flow

*Bing* I would like to point out the marked difference between the myocardium and the liver In the heart, the oxygen consumption varies directly with the coronary flow because the A V oxygen difference remains almost always constant and there is here quite a marked difference in the behavior of the two organs

*Bradley* What happens to the A V difference when oxygen consumption is extremely low?

*Myers* The A V difference is very high but the flow is so low that it does not help very much Many of these A V oxygen differences got up above 10 volumes per cent

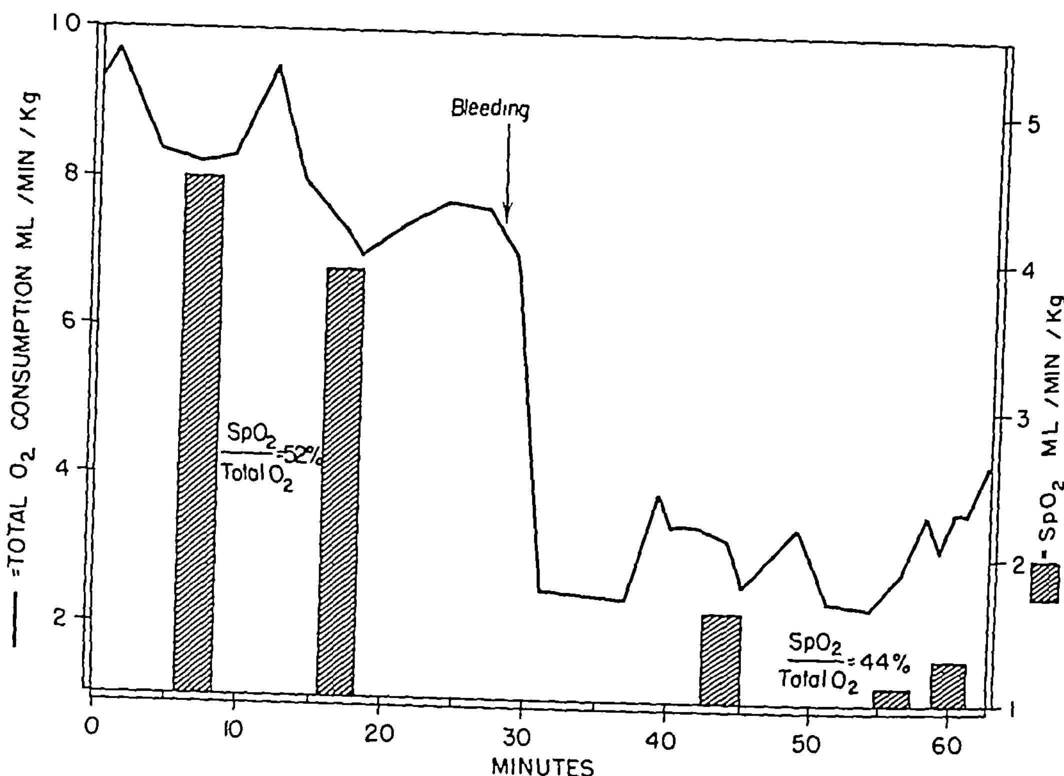



FIGURE 42 Effect of sustained shock, by bleeding a dog into a Lamson bottle set at 40 mm Hg, on total oxygen consumption and on splanchnic oxygen consumption

*Bradley* What happens to the extraction of BSP?

*Myers* With moderate hemorrhage and reduced splanchnic flow, the percentage extraction of BSP across the splanchnic circuit is increased Such dogs in general remove the same total amount of BSP per minute but they accomplish this at a considerably higher arterial concentration of the dye (Table V) With more severe hemorrhage, total BSP removal lessens in spite of a rising arterial blood concentration

*Merriman* How low does the hepatic venous oxygen go?

*Myers* It goes to about the same level in the bleeding experiment as it does in severe heart failure in man The maximal figures we have seen are in the neighborhood of 13 volumes per cent A-V difference in individuals or dogs which had normal hemoglobin concentrations and, therefore, arterial blood oxygen capacities of about 19 to 20 volumes per cent So about two thirds of the oxygen was removed at the slowest flows, not only in the dogs but in the individuals with most severe heart failure

*Remington* Is there a critical level of venous oxygen content at which the oxygen consumption first starts to fall?

*Myers* I cannot answer that question because the circumstances in which one gets this maximal extraction are difficult ones to attain We

TABLE V

Bromsulphalein Excretion in Dogs Before and After a Single Hemorrhage of from 32 to 65 Per Cent of the Estimated Blood Volume (Series of 13 Dogs)

| | Control | Hemorrhage | p Value |
|---|---|---|---|
| Corrected Infusion (Removal) Rate Mg/min/kg | 0 097±0 005* | 0 094±0 005 | >0 1 |
| Arterial Concentration Mg % | 1 60±0 18 | 2 12±0 23 | <0 01 |
| Hepatic A V Difference Mg % | 0 37±0 05 | 0 94±0 11 | <0 01 |

*Standard Error

tried to settle this issue and could not get consistent enough data on whether or not there was a critical level All I can say is that the maximal differences are generally the ones I just mentioned

*Merriman* In my experiments with hemorrhagic hypotension the total oxygen consumption remained normal if the mixed venous oxygen saturation was greater than 20 per cent In several experiments the mixed venous oxygen saturation was less than 20 per cent and the total oxygen consumption was reduced In a few animals the mixed venous saturation was 5 per cent, and the total oxygen consumption was 40 per cent of control

This reduced oxygen consumption may occur because certain organs can only extract oxygen until the capillary or venous blood is let us say 20 per cent saturated If the flow to these areas is markedly reduced its oxygen consumption will be less by the time the venous blood has reached this level of saturation and beyond which no further oxygen extraction can occur If at the same time the venous contribution from vascular beds which can extract oxygen almost completely is proportionately greater the resultant over all data will show a reduced total oxygen consumption and a very low saturation of mixed venous blood

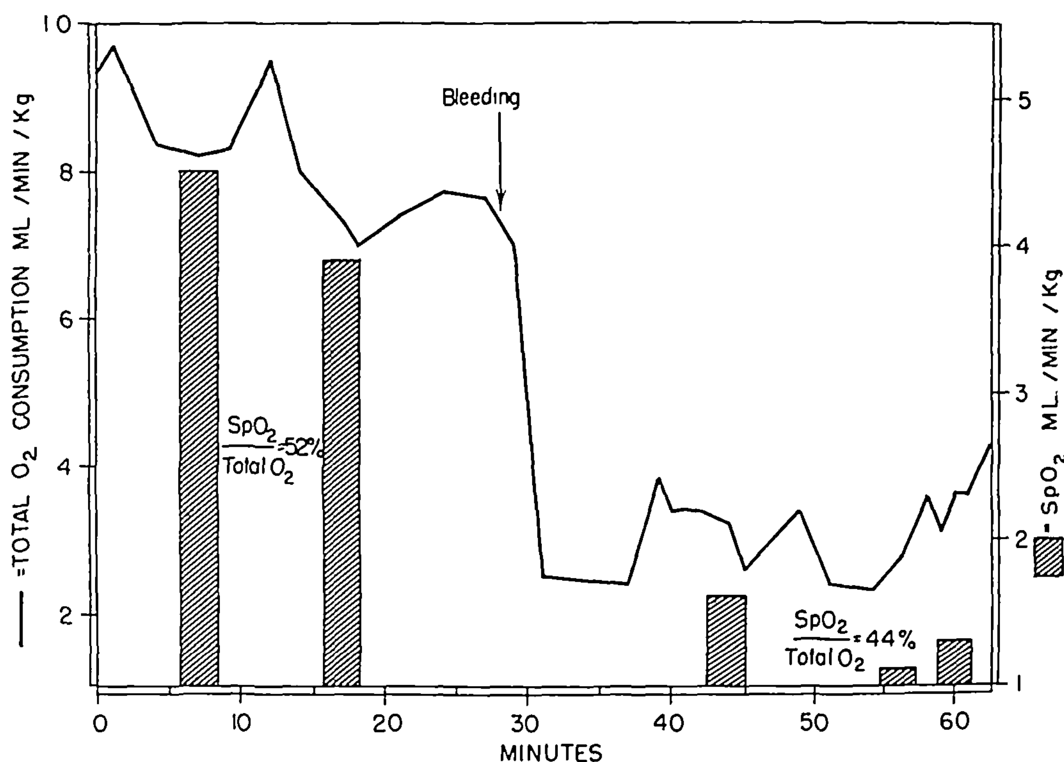



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## TABLE VII

**Mean Figures for Arteriovenous Oxygen Differences and for Splanchnic Oxygen Consumption in a Series of 11 Hyperthyroid Patients**

| | Arterial Mixed Ven O Diff Vols % | Arterial Hep Ven O Diff Vols % | Splanch O Consump ml min sq m | Splanch O Consump As pct of total O consump |
|---|---|---|---|---|
| Controls | 3.8 ± 0.2 | 4.3 ± 0.1 | 34 ± 1 | 23 ± 1 |
| Hyperthyroidism | 3.8 ± 0.2 | 6.3 ± 0.3 | 54 ± 2 | 28 ± 1 |

gives a considerably increased splanchnic oxygen consumption 54 ml min /sq M as contrasted to the normal figure of 33 or 34 ml

*Bradley* You don t mean there is a vasoconstriction do you? I think you mean that blood flow is reduced relative to flow elsewhere in the body

*Myers* Yes I should have put it that way Actually a good deal of the rest of the circulation is wide open such as the muscle skin kidneys and so forth

*Barcroft* Am I right in saying that Dr Kety found there was not much increase in cerebral blood flow?

*Kety* There was a slight increase in cerebral blood flow in one series (5) But the striking thing is that cerebral oxygen consumption is not increased (5 6)

*Bing* There is no change in oxygen consumption of the heart either in hyperthyroidism

*Shorr* As I remember the older figures of George Canby Robinson showed a rather smaller arteriovenous difference and I have been quoting those for years Shall I have to revise my opinion?

*Myers* You mean mixed A V difference?

*Shorr* Yes

*Myers* From my experience I would say yes You see the correspondence with normal values here I think what happens is that the very low A V difference that comes from places like skin and muscle balances out the increase in A V difference from the liver and the normally high A V differences from the heart and the brain and the result is a normal figure

*Remington* Would the same value hold in animals with anemia?

*Merriman.* I do not know None of my dogs had a significant degree of anemia

*Myers* In some of the human patients with severe anemia, the oxygen content of the hepatic venous blood would fall below one volume per cent Almost all of the oxygen was extracted in these severe anemic patients

The situation in hyperthyroidism is perhaps the most interesting one (Table VI) Here the splanchnic system behaves quite differently (4) The data presented were gathered from observations on fourteen individuals with hyperthyroidism, with an average increase in metabolic rate of about +50 as contrasted with control data The first column shows the expected increase in cardiac index The line underneath the mean figure indicates that the increase is significant to less than the one per cent level

The second column shows that the hepatic blood flow, expressed as milliliters per minute per square meter of body surface, is not significantly increased in this group of individuals with hyperthyroidism in spite of the increase in cardiac output Again, with mean arterial pressure not being significantly altered, this means that there is vasoconstriction in the splanchnic area

Table VII shows that the mixed A-V oxygen difference in hyperthyroidism is not changed but the hepatic A-V oxygen difference is very significantly increased This is in the face of a normal hepatic blood flow, and the product of this increased difference and the normal flow

## TABLE VI

**Mean Figures for Cardiac Index and Hepatic Blood Flow in a Series of 14 Hyperthyroid Patients**

| | Cardiac Index | Hepatic Blood Flow | |
|---|---|---|---|
| | l/min/ sq m | ml/min/ sq m | As pct of cardiac output |
| Controls | 3 9±0 2 | 810±24 | 19±1 |
| Hyper-thyroidism | 5 2±0 2 | 880±40 | 17±1 |

*Myers* This sort of observation then led us to make some studies of the effects of an increased metabolic load on this system and for this purpose we gave individuals amino acids intravenously (Figure 43) Fortunately we had a well tolerated semisynthetic mixture of amino acids which could be given intravenously without reaction Figure 43 illustrates the sort of situation found in a normal individual the hatched rectangle indicating 50 grams of amino acids in 5 per cent solution given intravenously The dark bars and squares show the hepatic blood flow, which is scaled on the left hand side This individual had a normal hepatic blood flow to start with and on the administration of amino acid there was no increase The hepatic A V oxygen differences are given at the top of Figure 43 this subject started with a reasonably normal figure and then more than doubled his A V oxygen difference so that the splanchnic oxygen consumption the open columns with the scale on the right hand side was considerably augmented Here is a situation then which is something like that in hyperthyroidism where one is doing more metabolic work as judged by oxygen consumption without any increase in hepatic blood flow

*Bing* What happened to the amino acid usage by the liver in those patients?

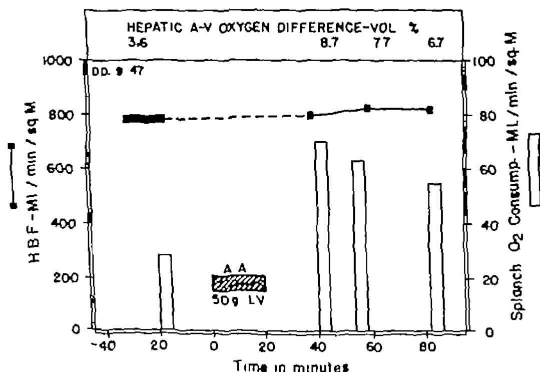



FIGURE 43 Effect of an amino acid mixture given intravenously on hepatic A V oxygen difference hepatic blood flow and splanchnic oxygen consumption in a control human subject

*Cournand.* What proportion of the total oxygen consumption increase in hyperthyroidism is accounted for by the increased oxygen uptake in the blood?

*Myers.* That will be shown to some degree in Table VIII, but first, Table VII shows the splanchnic oxygen consumption expressed as a per cent of the total, 28 *versus* 23 per cent, and that proves to be a significant increase, so that we have a greater percentage of the total oxygen being used in the splanchnic area in the hyperthyroid patient.

Table VIII shows that the hyperthyroid group had an increase in total oxygen consumption of +45 and an increase in splanchnic oxygen consumption of +64, so the liver, with no increase in flow, is accomplishing more work than usual and more work on the average than the rest of the body, and it is doing this by an increased oxygen extraction. Here is a situation in which the splanchnic area does not balance out its oxygen demands by an increase in flow.

*Barcroft.* There is a very large increase in muscle blood flow in hyperthyroidism and I wonder if it is known if there is an increase in oxygen consumption of muscle.

*Myers.* Dr. Wilkins, didn't you have some figures on oxygen difference?

*Wilkins.* No, we had them only on blood flow.

*Myers.* If blood is taken from the arm of an individual with hyperthyroidism, from either a deep or a superficial vein, the blood looks quite red. I presume this means a decreased A-V oxygen difference but I have not actually measured it, so I think that this flow is probably associated with a low oxygen extraction there.

*Shorr.* As I pointed out, Robinson has measured it and found it reduced in a few cases.

## TABLE VIII

### The Increase in Total and Splanchnic Metabolic Rates in Hyperthyroidism (14 Patients) as Compared to Normal Control Subjects

**Metabolic Rates at Time of Study**

| | Per cent increase above control group |
|---|---|
| Total MR | 45±5 |
| Splanchnic MR | 64±7 |

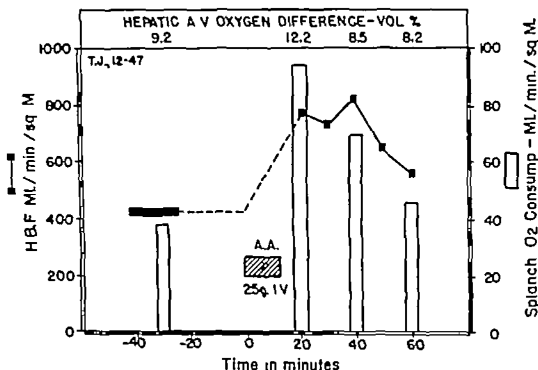



FIGURE 45 Same study as depicted in Figure 13 but done on a patient with aortic stenosis and congestive heart failure

400 ml /min./sq m a high A V oxygen difference 9 2 volumes per cent and a normal splanchnic oxygen consumption

With the administration of this dose of amino acids a doubling of the oxygen consumption temporarily resulted Of course the patient could not accomplish this well by an increase in oxygen extraction, having started with a base line A V difference of 9 2 and so in the individual with heart failure an increase in hepatic blood flow supervened Both the flow and the oxygen extraction were augmented to accomplish the increase in oxygen consumption in the splanchnic area

*Bradley* Did the blood pressure fall?

*Myers* No

*Bradley* The cardiac output?

*Myers* I do not know about cardiac output and that is an important question, but this experiment was so complicated that in spite of several attempts we were not able to obtain good data concomitantly on cardiac output and splanchanic blood flow Thus whether cardiac output went up or whether the same output was redistributed from other vascular beds to the splanchanic area I really cannot say

*Bing* May I ask whether or not you did similar tests on diabetic individuals?

*Myers* No we have not done this with diabetic subjects

*Myers* The amino acid usage goes up greatly and urea comes out, so I think these amino acids are deaminated, which is an oxidative process This is really a nonphysiologic technic of increasing oxygen consumption to see how the system may adapt to these circumstances

Figure 44 shows what happens in a cirrhotic individual It is very evident that this pattern is essentially the same as that of the normal person Perhaps there is some slight lag in the oxidation of the amino acids, as judged by the increase in oxygen consumption, but this is not striking It has been a quite consistent finding that the cirrhotic liver carries out this oxidative deamination of amino acids quite well and again without any significant increase in flow

*Shorr* Are these individuals decompensated?

*Myers* No, they were not strikingly decompensated For instance, none of them had ascites, but nevertheless they all had advanced cirrhosis

Figure 45 shows what happens when one performs this study on an individual with congestive heart failure The patient received only half of the dose of amino acids, as we did not want to give a cardiac patient the 500 ml volume of fluid This figure shows the same pattern that was shown earlier for heart failure—a low hepatic blood flow, about

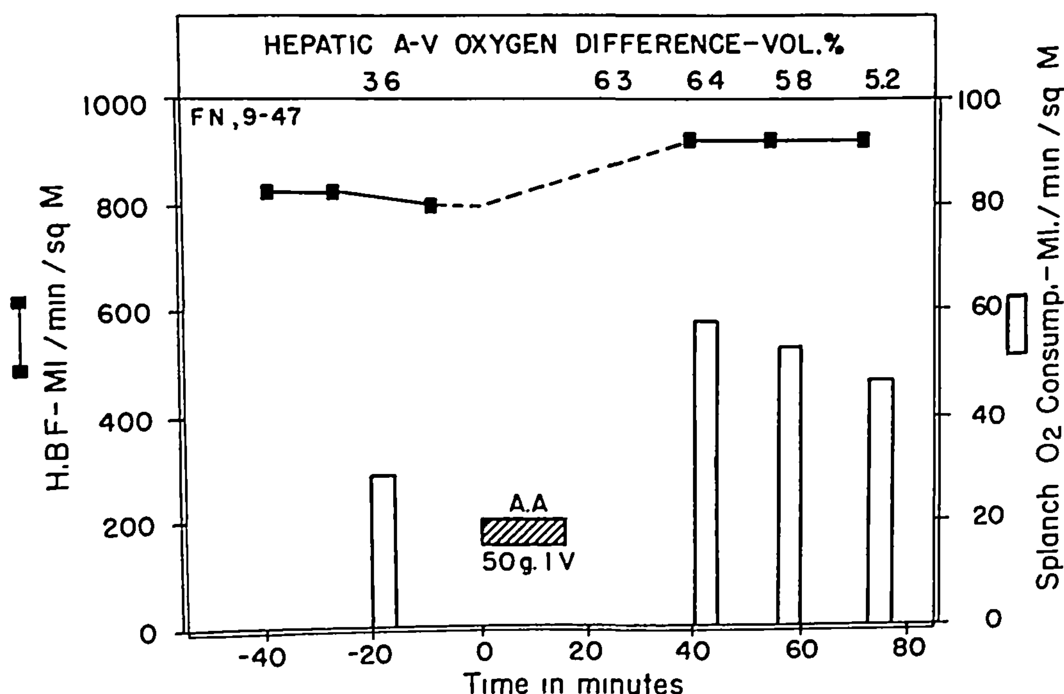



FIGURE 44 Same study as shown in Figure 43, but done on a patient with advanced but compensated Laennec's cirrhosis

quite a little because the splanchnic area under these circumstances takes up amino acids only with moderate efficiency.

These, then, are the patterns of response to amino acids which are comparable in many ways to those found in thyrotoxicosis, the system increasing A-V oxygen difference *in all instances unless flow should be* increased as in congestive failure.

*Selkurt:* Have you tried it in hemorrhage? Because of the markedly reduced flow following hemorrhage, one might expect the A-V difference to increase.

*Myers:* I do not know, Dr. Selkurt. We have not tried that; however, we have made other observations that would have to do with the adaptation of the splanchnic system, and these are to be shown in Table X. Figure 46 shows the pattern of these observations. The hepatic blood flow on the left is divided into high, normal, and low, and across the top is shown the per cent oxygen removed from the blood circulating through the splanchnic area—a low, normal, and high percentage removal. The cross-hatched squares indicate situations in which splanchnic oxygen consumption is maintained within the normal range. The three squares in the upper right-hand corner indicate increase in oxygen consumption, and those in the lower left, decrease.

With the above in mind we can see what happens in the various circumstances that we know about (Table X). An increased plasma

| | PER CENT OXYGEN REMOVED FROM BLOOD | | |
|---|---|---|---|
| | Low | Normal | High hypoxemia |
| HEPATIC BLOOD FLOW: High | | | METABOLISM INCREASED |
| Normal | METABOLISM DECREASED | | |
| Low | | | |

FIGURE 46. Schema for classifying various conditions according to hepatic blood flow (ordinate) and per cent removal of oxygen from the splanchnic circulation (abscissa).

*Bing* With the deficiency in protein synthesis in diabetes, you might obtain a different response of the liver to increased amino acid blood levels

*Myers*· Table IX shows what happens in the very severely anemic person As in the normal, the hepatic flow did not change significantly The A-V oxygen difference did not go up very much, again because most of the oxygen was already being extracted from the blood before the amino acids were given and, accordingly, there was no really significant increase in splanchnic oxygen consumption under the influence of these amino acids How long this small rise may have gone on, that is, whether the anemic individual eventually accomplished anything like the normal amount of hepatic oxidative deamination of the infused amino acids, I do not know These experiments did not go beyond one hour

*Nickerson* Was the rate of removal of amino acids from the blood stream comparable in the normal and in the anemic individuals?

*Myers* No, it was considerably reduced in the anemic subjects

*Nickerson* The amino acids persisted in the blood stream in the anemic patients?

*Myers* Not particularly, but the hepatic A-V difference of amino acids which we measured was much smaller than that in the normal individual

*Moe* And presumably they spilled more in the urine?

*Myers* I think they probably did, although the others also spilled

## TABLE IX

**The Response of the Hepatic Blood Flow, Hepatic A-V Oxygen Difference, and Splanchnic Oxygen Consumption in 3 Patients with Severe Anemia (Less Than 7 g of Hemoglobin) to the Intravenous Administration of Amino Acids**

| | 9 NORMAL | 3 ANEMIC |
|---|---|---|
| Hepatic Blood Flow | −5% | −5% |
| Hepatic A-V Oxygen Diff | +58% | +17% |
| Splanchnic Oxygen Consump | +51% | +13% |

keeping with the moderate increase in total oxygen consumption in the anemic state

The same thing is true of polycythemia where the per cent of oxygen removal is low because of a very high hematocrit but the oxygen consumption is within the normal range

Glucose gives the opposite result from amino acids not affecting flow significantly but decreasing A V oxygen difference so that splanchnic oxygen consumption actually goes down This requires a considerable amount of glucose 500 ml of 10 per cent Whether this high carbohydrate supply temporarily stops the normal oxidation of amino acids I do not know but that would be one possibility

On the right hand column of Table X are listed hyperthyroidism amino acids and leukemia in which flow is normal but the A V oxygen difference is high These are of course cases of leukemia without marked anemia It might be of interest that about two thirds of the increase in total oxygen consumption that one finds in individuals with such diseases as chronic myelogenous leukemia can be accounted for in the splanchnic area

*Stead* Is this related to the size of the spleen?

*Myers* These were individuals with chronic leukemia and big spleens and livers

In the lower right hand corner of Table X are the situations where flow is low and A V extraction is high so as to give normal oxygen consumption There are question marks before hepatitis and obstructive jaundice because we have no flow measurements in individuals suffering from such diseases since there is not a satisfactory technic for this But as this chart would indicate the A V oxygen difference in both circumstances is considerably increased This would mean either that the oxygen consumption was normal if the flow was low or the oxygen consumption in the splanchnic area was increased if the flow was either normal or high It is a matter of pure conjecture as to which may be the case I have chosen to believe that the flow is probably low and that the A V oxygen difference goes up compensatorily In severe hepatitis where there is considerable hepatic necrosis as judged by the clinical course, liver biopsy and so forth the A V oxygen difference is normal and sometimes quite low That corresponds with the fact that such badly damaged livers are not able to use much oxygen at all but it should be emphasized that these are individuals with very severe hepatitis and usually with quite a poor prognosis

These then, are the relationships that I would draw between flow and oxygen removal and oxygen consumption it is evident that there are many different patterns We must recall as I pointed out to begin with

volume as induced by human serum albumin or dextran, for example, sometimes gives an increase in flow with a low A-V oxygen difference We might also put in the upper left-hand square the observations Dr Wilkins made post-sympathectomy, where the same pattern was seen

Pyrogen, even in subfebrile doses, will give an increase in flow with at least a nomal oxygen extraction and, therefore, an increase in oxygen consumption, and epinephrine generally does the same thing

In Table X, "anemia" is in parentheses The percentage of oxygen removed from this blood is high, and the actual absolute A-V difference is low, the parentheses are there to draw attention to that fact In the anemic individual the A-V oxygen difference and the flow go in opposite directions, as I indicated previously, but the splanchnic oxygen consumption is actually moderately increased above the normal range, in

## TABLE X

**Various Conditions Classified According to the Schema of Figure 46**

| Hepatic Blood Flow | Per Cent Oxygen Removed From Blood | | |
|---|---|---|---|
| | Low | Normal | High "hypoxemia" |
| High | Increased plasma volume - variable | Pyrogen<br>Epinephrine | (Anemia) |
| Normal | (Erythremia)<br>Glucose infusion | Normal<br>Portal cirrhosis<br>Diabetes mellitus<br>Hypertension<br>Pregnancy | Hyperthyroidism<br>Leukemia<br>Amino - acids |
| Low | | Myxedema<br>Portal cirrhosis | Cardiac failure<br>Portal cirrhosis<br>?Hepatitis<br>?Obstr jaundice<br>Orthostasis<br>Exercise<br>Anesthesia |



FIGURE 47 Roentgenogram of a venous catheter wedged in a small hepatic vein of the right lobe of a normal human liver

eter so placed Some of these data are conjectural some of them are real and some of them are real but from more than one source I would begin by pointing out the pressure in the hepatic vein the free hepatic venous pressure shown next to the catheter is a low one in our experience about 3 mm. Hg The pressure that builds up in the obstructed segment in normal individuals on the average has been 5 mm Hg

that we really do not know anything about the portal venous oxygen content in any of these circumstances, except in the case of the cirrhotic patients, and that the question of how much of the splanchnic oxygen consumption is used in the portal viscera and not in the liver remains a problem

*Moe* Do you have any way of knowing whether or not the hepatic artery and portal vein both participate in the increased hepatic blood flow caused by epinephrine? The blanching of the intestine which is so characteristic in the experimental animal, implies a diminution of mesenteric and portal blood flow Dr Green, when you inject epinephrine intravenously in the dog doesn't the blood flow in the mesenteric vessels decrease?

*Green* Epinephrine injected into the mesenteric artery of dogs will decrease flow in the mesentery just as it does in the skin and muscle There is a reversal of the epinephrine effects in the gut with adrenergic blockade just as there is in skin and muscle

*Moe* But lesser in degree

*Green* A little lesser in degree but it is still very important

*Moe* I hope you will also study the blood flow responses of the visceral circulation to intravenous epinephrine

*Green* Possibly the dog's gut is different from man's gut just as the dog's skin and muscle are different from man's

*Myers* I believe there are some animal studies which would suggest that the hepatic arterial flow is increased by epinephrine (7, 8, 9) But from human studies one couldn't draw any conclusion at all

*Stead* Dr Wilkins, did you make any epinephrine studies on sympathectomized people

*Wilkins* No I didn't

*Myers* In human subjects, the cardiac output is increased considerably by epinephrine, which is another factor that must be taken into account

In the lower right-hand corner of Table X one should add, of course, hemorrhage and fainting, which are not there

FLOW AND PRESSURE RELATIONSHIPS

The second phase or facet of the problem has to do with some pressure relationships in the liver and the splanchnic area Figure 47 is a roentgenogram, which shows a catheter wedged into a small hepatic vein for the estimation of the pressure which builds up in the occluded vein This catheter is placed in much the same way as catheters are wedged for estimation of the so-called pulmonary capillary pressure Figure 48 is a schema of the normal splanchnic circulation with a cath-

that the pressure here is about the same as it would be in other parts of the body

*Cournand* Can you ascertain the direction that your catheter takes in relation to the reference point? You could have marked variation of the position anteriorly or posteriorly

*Myers* Yes one does have quite a marked variation but it varies considerably from one person to another and I think that may have a small effect on the gradient between the obstructed segment and the free hepatic vein however in a series I do not think this will be too disturbing a factor

*Bing* What is the right atrial pressure?

*Myers* The right atrial pressures were the usual pressures which varied from a few millimeters negative to a few millimeters positive but there was a small positive gradient of a few millimeters of mercury from the hepatic vein to the right atrium

We might comment a bit on this figure of 5 mm Hg in the obstructed segment I use the term obstructed perhaps not correctly in that if blood is withdrawn from the small area with a catheter firmly wedged in, there is no evidence of stagnation of blood and in that the oxygen content of this blood is the same as the oxygen content of free hepatic venous blood and the glucose content of this blood is likewise the same

Redder blood or blood with less sugar can be obtained by sucking a little harder but that is an artifact

In making injection studies of livers and studying areas where the catheter is wedged which is away out peripherally as the roentgenogram (Figure 47) shows it is found in general that one is dealing with what one might call an end vein in that there are no large anastomoses that run from one vein of the size we would occlude to neighboring veins of the same caliber

Nearer the large hepatic veins or the vena cava there are many large venous intercommunications but out along the periphery of the liver we were completely unable to demonstrate any veno-veno shunts so to speak however there may be some small ones that the injection technic (we used Liebow s technic (10) ) did not demonstrate

We would think this low pressure in the occluded segment would depend upon a fairly free sinusoidal anastomosis with the neighboring segments of the liver and the low pressure would indicate that the hepatic circulation normally is a very low resistance one Perfusion studies would bear this out Under quite low pressures fluid can be perfused very easily from portal vein to hepatic vein or for that matter the fluid can be reversed from the hepatic vein to the portal vein Hepatic arterial perfusion is a much more difficult matter of course I think the figure of 5 mm Hg then is dependent on a low resistance in the venous and sinusoidal system with fairly rich small vessel anastomoses

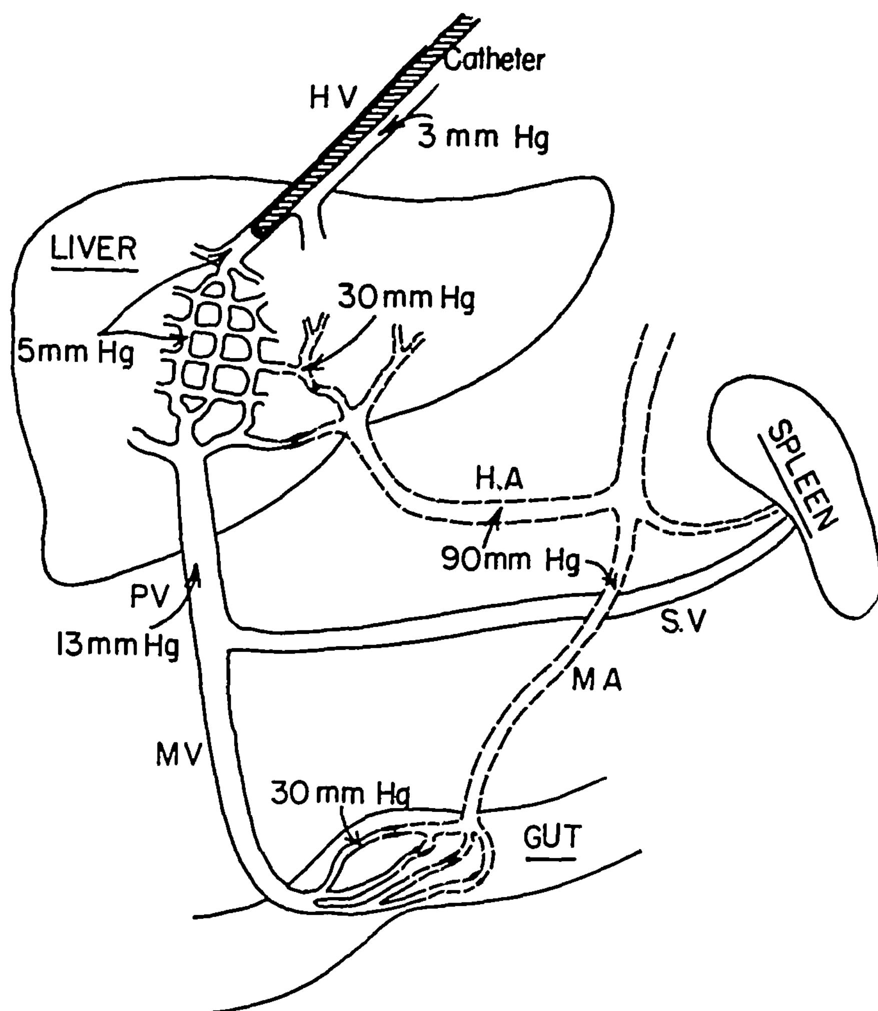



FIGURE 48 Schema of the normal hepatic circulation

*Wilkins* These measurements all refer to the same level of atmospheric pressure?

*Myers* They all refer to the same level of atmospheric pressure

*Bradley* What was the reference plane?

*Myers* The usual reference plane

*Bradley* Not the tip of the catheter itself?

*Myers* No, not the tip of the catheter, the estimated middle of the right atrium, i e , 10 cm anteriorly from the posterior thorax

The pressure of 13 mm Hg is the average figure obtained from the literature where surgeons have estimated portal venous pressure I emphasize that this is a surgical estimation and may or may not be representative of the true physiological portal venous pressure in man which, so far as I know, has never been really accurately estimated

The figure of 30 mm Hg for the hepatic arteriole is an assumption

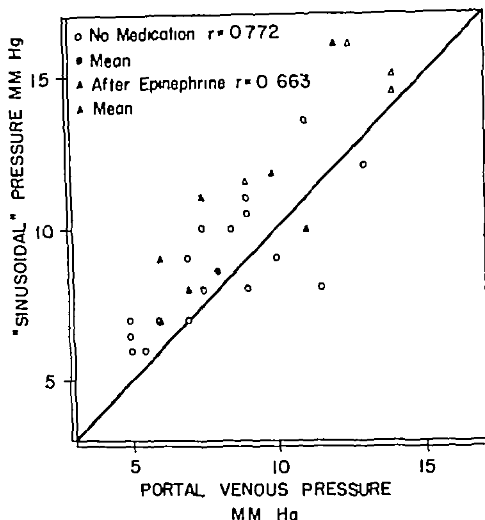



FIGURE 49 Hepatic sinusoidal pressures in cats compared with directly and simultaneously measured portal venous pressures, before and after administration of epinephrine into the portal vein.

anesthesia then the catheter was brought out through an established wound in the abdomen and the animal was allowed to recover The portal venous pressure was measured with the abdomen open and figures were obtained similar to those that the surgeons give for the portal venous pressure in man But after the animal had recovered and the effects of anesthesia had worn off the portal venous pressures fell down to less than 10 mm. Hg that is to the same general range that we are recording for our sinusoidal pressures in the cat or for that matter in man So I would raise the question as to whether portal venous pressure in intact man is not really a fairly low value much lower than any of the surgical estimates would have us think and that the sinusoidal pressure or wedge pressure is a reasonably good index as to what this portal venous pressure actually is

*Burton* Do you think the sinusoids can be permeable to water and electrolytes? I was wondering how you could have osmotic equilibrium if they were at a pressure of 5 mm Hg They probably, then, are not permeable to water and electrolytes

*Bradley* As a matter of fact, they are very permeable, indeed

*Burton* How do you obtain osmotic equilibrium with a capillary system—

*Bradley* Because they are also permeable to protein Hepatic lymph, for example, has essentially the same protein concentration as the blood plasma

*Myers* I do not think we should be concerned about this gradient of 13 mm Hg in the portal vein to the 5 mm Hg in the occluded hepatic vein without more careful inspection of the data

Figure 49 shows some results obtained from experiments on cats These animals were used because they were convenient and also because there are some older studies that indicate that the cat's liver, so far as the circulatory setup is concerned, is not too unlike the human liver Here we are contrasting the pressure in the occluded hepatic vein, the wedge pressure, or the "sinusoidal" pressure, with the directly measured portal venous pressures in anesthetized cats with the abdomen open The heavy line is the line of perfect agreement You will see that there is actually quite good agreement between the directly measured portal venous pressure and the "sinusoidal" pressure This is true both before and after epinephrine was put into the portal vein to raise portal venous pressure Actually, most of the sinusoidal pressures are slightly higher than the portal venous ones, although not significantly so statistically This could be caused by the fact that in one case, the wedge pressure or "sinusoidal" pressure, the recording system pointed against blood flow and in the other case, the portal venous pressure, it pointed with blood flow, so that so-called end pressure would be added onto "sinusoidal" pressure but subtracted from venous pressure measurements

The important thing is, though, that there is quite good agreement in the cat between the two pressures and this would make us think that the "sinusoidal" pressure is quite representative of the portal venous pressure and that, actually, there must be a fairly small gradient between the portal vein and the free hepatic vein Dr Fine and some of his colleagues (11) found much the same situation in dogs a few years ago

Recently, Dr Maurice Visscher* described to us some experiments on dogs in which small catheters were put into the portal vein under

*Personal communication

where fibrotic changes occur do the openings in the sublobular veins have adequate smooth muscle to account for the epinephrine effect?

*M Knisely* I would like to say a word or two on the hepatic outlet valve mechanisms of the liver Miss Fann Harding in our laboratory has been studying the outlet sphincter mechanisms * In brief blood returns to the right heart by three major pathways the superior vena cava the inferior vena cava and the hepatic veins There are flap valves in the first two permitting forward blood flow only The hepatic outlet valves are sphincters the only sphincters which can restrict or stop blood flow toward heart

Krogh et al (13 14 15) demonstrated that the *human* liver and the portal vein bed could store and release blood and thereby limit and control the rate of the filling of the heart and the cardiac output The pooling of blood in the liver and the portal vein causes one type of circulatory shock

The three known types of hepatic outlet valves are (*a*) in dogs hepatic veins contract (16 17) (*b*) in several species a cluster of hepatic sinusoids join together draining to a central vein through a single sphincter (18) and (*c*) in frogs and rhesus monkeys each sinusoid or small group of sinusoids drains through a single outlet sphincter into a central venule (19) Single sinusoid outlet sphincters and Deysach s small sluice channels have now been seen in the living livers of frogs rhesus monkeys mice rats cats hamsters guinea pigs rabbits and dogs Warner (20) reported (in guinea pigs) structures resembling myofibrils within the cytoplasm of cells like smooth muscle cells surrounding sinusoid efferent ends In frogs the contractile tissue fluoresces differently from parenchyma

Dr Fine you have made discoveries along this line As I don t know the literature from your laboratory I wonder if you would tell us a little about your work

*Fine* We did not observe any localized sphincter action in the liver but an over all vasoconstrictor effect

*M Knisely* Of the whole venous system?

*Fine* The entire venous system

*Bradley* These catheters should be well beyond any such throttle system Isn t that right, Dr Richards? Where were the throttles in your experiments

*Richards* They were quite near the outlet Actually the effect of epinephrine was not very strongly apparent except as a reversal of the effect of histamine When histamine was given, then the sluice clos-

* These studies were aided by U S Public Health Service Grant H 1683(C)

*Selkurt* If the output of the sinusoids is blocked by wedging, there may be a tendency to build up pressure because of the contribution of the hepatic artery This may contribute to an elevation of portal pressure What role do you think the hepatic artery plays in this?

*Myers* Naturally, we thought about this Since the hepatic artery pours into a low-resistance system, I would think that, in the nomal liver where there is no wedging, the hepatic artery has about as much effect on the pressure in the sinusoid as does a patent *ductus arteriosus* when it empties into the pulmonary arterial system The resistance to outflow is so low that the pouring in of hepatic arterial blood under an arteriolar pressure of 25 to 30 mm Hg has hardly any effect on the sinusoidal pressure

When one wedges, I think that what happens is that the pressure rises to a level which is dependent in good part on how rich the small vessel anastomoses are to neighboring areas One is still dealing with a low-resistance system except that by blocking the vein of a compartment, it so works out that the pressure that is built up in the occluded system rises fairly closely to that in the portal venous afferent, the arterial pressure is still dissipated, so to speak, in the low resistance system I think we are dealing in our system with a great many sinusoids and I think we have some of them at one stage of opening or closing and some at another and they pretty well balance each other out, so that by random selection we end up with a mean situation which provides this sort of measurement

*Nickerson* I am not quite sure how to interpret this effect of epinephrine In general, the correlation between wedge pressure and portal venous pressure is not as good after the epinephrine, and the wedge pressure tends to be a bit higher Is this a local injection?

*Myers* No, the epinephrine was given into the portal vein

*Nickerson* The action of epinephrine would seem to be on the large veins beyond the point at which the wedge pressures are measured, but I am not sure just where this would be

*Myers* The same thing has puzzled us

*Moe* Doesn't the cat have hepatic vein sphincters?

*Myers* That is the dog

*Nickerson* If this were a dog, it would be easier to explain Have you any definite thoughts as to where the epinephrine is acting?

*Myers* No, I have not except to point out that there is evidence, going back to Burton-Opitz (12) in 1912, that epinephrine administered into the portal vein causes constriction of small intrahepatic blood vessels

*Nickerson* From a functional standpoint, as distinct from cirrhosis

drugs does not apparently reside simply in a general blunting of vasoconstrictor reactions during shock. Evidence for this thesis was obtained when shock experiments were carried out in rats pretreated with dibenzyline. Rats were prepared for study according to the Engel technic (23) whereby the intestinal viscera were removed leaving the hepatic artery intact as the sole supply of blood to the liver. In such eviscerate preparations dibenzyline was found to be effective in preventing the lethal outcome of a standardized hemorrhage procedure. When, in addition, the liver was excluded from the circulation, dibenzyline no longer had a protective action. Other agents, such as chlorpromazine, did, however, protect against circulatory collapse even in the absence of the liver. The protective action of dibenzyline would therefore appear to reside in some circulatory or metabolic change in the liver proper. Whether the drug acts on the sluice mechanism of the hepatic veins is difficult to ascertain.

*Fine:* We do not believe that the vasoconstriction in the liver in hemorrhagic shock is substantially influenced by any adrenergic blocking agent.

*Bradley:* In hemorrhage in dogs (24) we found little evidence of vasoconstriction in the liver. The blood flow seems to fall in relation to the fall in blood pressure.

*Fine:* We visualized the circulation in the liver with roentgenograms made after *in vivo* injection of an opaque medium into the portal vein before and during shock (25, 26, 27, 28). There is a rough inverse correlation between the diameter of the vessels and the portal pressure.

*Bradley:* Do you think the diameter you are able to measure in this way is the diameter that is relevant to the question of resistance to flow through the liver?

*Fine:* The fact that there was a decreased diameter—

*Bradley:* We have evidence, you see, that the blood volume in the liver greatly decreases, which means that the volume of blood in the vessels decreases. As a consequence one might expect the visible vessels to diminish in size, but this does not mean necessarily that the resistance to flow through the vessels is greatly increased. As a matter of fact, the major resistance must reside at the arteriolar and venular level.

*Green:* In the dog, epinephrine, arterenol, and splanchnic stimulations are all quite equally effective in reducing the blood flow in the mesenteric artery and in causing a slight rise in the portal pressure. The resistances calculated from the aorta to the portal vein and from the portal vein to the vena cava rise approximately equally in both those circuits (29, 30). When gradually increasing doses of the adrenergic blocking drugs are given, the response of epinephrine is converted to

ed down abruptly and the liver swelled up to great size, at that time the "sluice" could be opened again by more epinephrine This action occurred only in dogs and was demonstrated by actually grossly cutting out the hepatic vein area quite close to the hepatic vein orifices, following which the "sluice-effect," or "throttle-effect," disappeared, so that it appears to be a rather large-vein affair This was as far as the experiments went, then on cats and goats the same thing was tried and nothing happened at all, no such mechanism was found (16)

*M Knisely* As I said, Miss Harding, in our laboratory, has found specific contractile outlet sphincters at the outlet end of individual sinusoids in the living livers of frogs, rhesus monkeys, mice, rats, cats, hamsters, guinea pigs, rabbits, and dogs We know what kind of structures to look for but now we must look in each species of animal to see which kinds of sphincters are present in each, and we must study the physiology and pathologic physiology of each species to see what reactions of each kind of contractile mechanism occur during each kind of condition

*Nickerson* Dr Knisely, do you know if these small sphincters on the sinusoids respond to epinephrine in the same way as the hepatic sphincter in the dog?

*M Knisely* Dr Edward Bloch (21) published an abstract of work he was doing on the responses of the outlet sphincters to epinephrine and acetylcholine The work, however, was interrupted by the war It is obvious to one who reads his abstract (21), that the whole subject of the pharmacological responses of the three different types of hepatic outlet sphincter control mechanisms is now open for careful investigation

*Lamport* Is the difference in correlation coefficients definitely significant?

*Myers* No, it is not

*Wood* Dr Donald Balfour and his group (22) in California have been interested in the measurement of hepatic wedge pressure and in the study and diagnosis of portal hypertension and the effect of portacaval shunts, he has reported to me that there is a very good correlation between hepatic wedge pressure in patients with portal hypertension and the pressure that is recorded at the time of operation for portacaval shunts

*Myers* I am coming to this in a few minutes

*Shorr* I was wondering what the effect of adrenergic blocking agents in shock might be with respect to resistance to blood flow through the liver

*Zweifach* The mechanism of protection by adrenergic blocking

The latter had either a normal or an above normal hemoglobin content We were careful to rule out myoglobin in these determinations

*Burton* May I ask if anyone has yet measured whether or not the liver is actually anoxic in shock? I have sat in these conferences for 2 or 3 years and noted that a whole scientific empire seemed to be built up on the theory that irreversible shock was in some way connected with ischemia and anoxia of the liver and I always wondered whether or not there was evidence that the liver *was* actually ischemic and anoxic now Dr Bradley does not seem to think it is

*Bradley* I didn t say it wasn t

*Shorr* Dr Myers has just shown that it is

*Burton* Other people think that they have shown it but it seems to be a matter of debate If it is still debatable it is a most unsteady foundation on which to build all this planning of research into what might happen in the liver if it was very anoxic

I am wondering if Dr Montgomery s polarograph will not be a very great help Do you think Dr Montgomery you could measure oxygen tension in the liver with the polarigraph during shock?

*Montgomery* It has been done in a preliminary way by Charles Wolferth, Jr and Dr Andrew Boyd Jr (32) under Dr William Fitts sponsorship (Table XI) They put such electrodes in the liver and produced acute hemorrhagic shock meaning a 70 mm Hg blood pressure and found that the oxygen tension of the liver was maintained whereas that of the skin and muscle both fell They made simultaneous measure

TABLE XI

Average Oxygen Tension

(Expressed in Galvanometer Units, Measured Polarigraphically)

| | Liver | Muscle | Skin |
|---|---|---|---|
| Intact Hepatic Circulation (10 dogs) | | | |
| Before lowering B P | 50 | 57 | 74 |
| 70 mm Hg for 1 hour or more | 55 | 35 | 51 |
| Chronic Ligation of Hepatic and Gastroduodenal arteries (5 dogs) | | | |
| Before lowering B P | 48 | 55 | 71 |
| 70 mm Hg for 1 hour or more | 50 | 34 | 53 |

Adapted from data of Dr Charles Wolferth, Jr and Dr Andrew Boyd, Jr

one of dilation but the constrictor response to arterenol is gradually reduced, if high enough doses are given, both the constrictor and dilator responses are abolished

*Bradley* I am not questioning the capacity of the liver to undergo vasoconstriction that can increase the resistance to blood flow through it, I am simply raising the possibility that there may not be an increased resistance to flow during shock at a time when there is a decreased capacity of the total vascular bed of the liver to hold blood

*Fine*· As shown in some of our earlier data (25) on blockage in the liver, when we transfused the animal to restore blood volume but had no success in restoring the circulation, we kept on transfusing to see whether a plethora would somehow or other restore the circulation This achieved nothing except a hemoperitoneum The belly actually swelled so that we could withdraw liters of blood from the peritoneal cavity That was the only place where the infused blood seemed to collect Of course we ruled out rupture of vessels as an explanation of the hemoperitoneum This is indirect evidence, it seems to me, of blockade in the liver

*Shorr* Doesn't one of the differences lie in the degree of shock which you were producing?

*Bradley* It may be

*Fine* May I add one more point? When we did this procedure on dogs that had an Eck's fistula and were in shock, we avoided the hemoperitoneum as well as hemorrhage into the intestine

*Richards* Didn't you also demonstrate a dilated portal vein at the same time that the rest of the liver was small?

*Fine* Yes, that is to say the vasoconstriction involved the entire intrahepatic vascular bed, but the segment of portal vein outside the liver, i e, between the liver and the gut was distinctly dilated, indicating a passive distension of the portal vein

*Myers* I think the discrepancy is probably due to the degree of shock, because our findings were the same as Dr Bradley's, there was no increase in resistance to flow Also, I think perhaps Dr Fine studied more severe degrees of shock than we observed from these single hemorrhages

*Bradley* We had hoped we would find, in the animals that were apparently dying in irreversible shock, some evidence of pooling of blood in the splanchnic bed This we failed to find, perhaps because we failed to overload with transfusions to the proper extent

*Fine* I might refer to some of our early studies (31), on the hemoglobin content of different tissues in animals dead of hemorrhagic shock All tissues (and this may bear on Dr Montgomery's question, too), except liver, kidney, spleen, and lung were virtually ischemic

the hepatic vein blood by means of which the mean capillary pressure of oxygen in the liver can be calculated Otherwise we are never sure whether there is anoxia or not Ischemia and anoxia are not identical terms

*Myers* Although these very high hepatic A V oxygen differences and the reduction in splanchnic oxygen consumption are not proof that the oxygen tension is low I think it is very difficult to reason otherwise and then when this is combined with the fact that not infrequently under circumstances of shock just as in other anoxic states central lobular necrosis is observed it is hard to avoid the conclusion that the liver in shock is anoxic

*Selkurt* Some estimates of liver blood flow in hemorrhage and shock have been made based on the BSP method Although reductions in flow have been observed this method might be thought of as revealing minimal flow changes under circumstances of hepatic anoxia Based upon some experiments we have done in which we studied the effect of complete hepatic ischemia on subsequent dye removal it was observed that the A V dye difference and the extraction ratio were reduced following ischemia. In the face of other evidence of reduced blood flow this would yield erroneously high calculated hepatic blood flow In truth the blood flow might be much less than the BSP method would show which would again emphasize the fact that during shock reduction in blood flow must be quite great in the liver

*Bradley* The blood pressure falls to the same extent as the blood flow

*Selkurt* That would be a minimum change

*Burton* Dr Montgomery has told us the direct measurement did not seem to show that the oxygen tension in the liver fell

*Montgomery* I think there are probably several degrees of shock if not several kinds of shock and that was the finding by these investigators in their bled dogs but I do not think it necessarily follows that the livers of Dr Fine s dogs had normal oxygen tension

*Zweifach* The animals to which you refer were kept at a blood pressure of 70 mm. Hg whereas those of Dr Fine were maintained at 35 mm Hg

*Shorr* It is borne out by the BSP data that at 70 mm Hg the blood flow does return to normal It is below that level that it is significantly reduced

*Selkurt* What were your pressure levels and how long did you hold them?

*Bradley* Usually below 30 mm Hg and they were held there by repeated blood letting

ments of blood flow through muscle, and they stated that the decreased oxygen tension could be accounted for by vasoconstriction and decreased blood flow Perhaps none of the measurements were in animals in "irreversible" shock

*Fine* There are additional data, Dr Burton First of all, the oxygen content of portal vein blood has been measured * It varies between 1 and 5 volumes per cent in a well established case of severe hemorrhagic shock That should give some index of the oxygen supply reaching the liver The hepatic vein blood is also very low in oxygen content

*Burton* I still think that someone should measure the oxygen tension directly, because it seems to me this is a very important point and there obviously is considerable debate on it I am quite neutral in the matter, but I doubt if we have a very firm foundation on which to build our theories

*M Knisely* I would not know what a definition of anoxia of the liver would be However, we have seen areas of the liver in which there is no blood at all, and none comes in

*Burton* Under what circumstances?

*M Knisely* The animal is given a small hemorrhagic shock, following which this sequence of events is observed The hepatic artery and the portal vein contract until they are tightly shut, neither has any lumen The inlet sphincters of the sinusoid shut off and then the sinusoid goes through a peristaltic contraction, pushes all the contained blood out to the central vein, and the outlet sphincter shuts off

I do not know where you want to measure the concentration of oxygen in blood in order to determine there is no blood in the liver in that area but such things do happen

*Burton* This does not agree with the clinical observations made in Korea on the state of the liver in patients who have died of shock, does it?

*M Knisely* I do not know about the observations made in Korea, but I believe there are at least six different mechanisms of shock, any one of which is capable of causing death

*Bradley* Don't you think Dr Myers' data show there is a considerable degree of anoxia?

*Bing* Much of the difficulty seems to arise from the use of the terms "anoxia" and "ischemia" (33) They are not synonymous and the difficulty arises from the statement that if there is a decrease in oxygen consumption of any organ that this organ must be anoxic That is not so, and the only sign of anoxia we have here is the oxygen tension of

*Seligman, A M, Frank, H, and Fine, J *Unpublished observations on oxygen content of portal vein blood*

controls rose to an average of 3 7 mg per cent Eventually circulation in the terminal vascular bed deteriorated VDM (ferritin) was found in the blood and these control dogs became unresponsive to transfusion of the shed blood In contrast to this picture in dogs with arterialized liver and with comparable degree and duration of hypotension the uric acid values in plasma rose no higher than an average of 2 4 mg per cent So if the plasma uric acid values reflect the state of oxidative metabolism of the liver then in the control dogs the liver must have been if not anoxic at least quite hypoxic Also these observations indicate that the failure of plasma uric acid to rise to the same height in the dogs with arterialized liver must have been caused by the continuation of more effective oxidative processes in the liver as a result of the improved circulation brought about by the operation I might add that in the dogs with the arterialized liver the circulation in the terminal vascular bed remained relatively good and the large accumulation of VDM (ferritin) in the plasma which we ascribe to an hypoxic liver did not appear The dogs recovered following transfusion

*Selkurt* There is one other consideration In hemorrhagic shock portal pressure is elevated it may begin to rise during the hypotensive phases of hemorrhage and it is markedly elevated upon transfusion of blood following a period of hypotension Contributing to this rise might be an increase resistance to flow through the hepatic channels Whether this is due to vasoconstriction or some other mechanism can not be said

*Short* Or increased intraheptic pressure whatever the mechanism is

*Selkurt* Whatever the mechanism it is hard to say exactly what causes it but there exists this evidence of increased hepatic vascular resistance

*Fine* Would the functional behavior of the liver be useful to you Dr Burton, in determining whether or not the claim of anoxia is valid? We made direct determinations of liver function, not by such methods as deamination of amino acids but by measuring the rate of synthesis of substances that are made exclusively by the liver fibrinogen and prothrombin The difference between this test and the test of deamination as a measure of liver function is that deamination can be achieved by many tissues other than liver while the synthesis of fibrinogen or prothrombin cannot

As a measure of the degree of liver injury it is important to note that a gross disturbance in the capacity of the liver to make these substances is present within one hour after inducing severe hemorrhagic shock

*Burton* I certainly would accept that as showing dysfunction, prob-

*Bing:* Were any of these done in normovolemic shock, that is, after the withdrawn blood had been reinfused into the animal? Did you see irreversible changes then?

*Bradley:* We transfused a number of the animals and the blood pressure and hepatic blood flow returned to normal. These were animals that survived. There was also no change in those that did not survive once splanchnic blood volume had decreased.

*Richards:* Is there any great rise in lactic acid or other acid products?

*Myers:* Lactic acid does go up in the blood considerably.

*Richards:* Out of proportion to the amount of lactic acid generally found in the blood?

*Fine:* Yes.

*Selkurt:* Blood amino acid concentration goes up.

*Bing:* Pyruvic acid rises also.

*Shorr:* In dogs, the blood uric acid values reflect the degree of oxidative metabolism of the liver, since these values are maintained at their normal low level through the oxidation destruction of uric acid by the liver. When the liver becomes hypoxic, the uric acid values rise. According to the studies of Van Slyke (34), the reduction of blood pressure by hemorrhage to about 70 mm. Hg is not accompanied by a rise of blood uric acid values. From this we may infer that the liver metabolism is still aerobic. However, when this investigator lowered the blood pressure to 30 mm. Hg, there was a sharp rise in blood uric acid. We can corroborate these findings from our own studies on animals in hemorrhagic shock.

*Baez:* With respect to plasma uric acid values as an index of liver hypoxia, I should like to describe our observations* of uric acid changes during hypotension in normal dogs and in dogs with arterialized liver. Liver arterialization was achieved, following excision of the right kidney, by anastomosing the peripheral end of the divided portal vein to the right renal vein and joining the renal artery to the hepatic end of the portal vein by means of an artery graft (35). Dogs that were successfully operated upon survived in good health for many months. The operation itself did not alter the basal values for uric acid (average 0.5 mg. per cent). Comparative studies were made of plasma uric acid levels in these animals and in normal controls during a standard hemorrhagic procedure. In the normal control dogs, when the blood pressure was lowered to about 70 mm. Hg by blood withdrawal, there was only a small increase in uric acid; however, when the pressure was reduced, by further bleeding, to 40 mm. Hg, the plasma uric acid in the

*Baez, S., Taussky, H. H., and Shorr, E. Unpublished data.

is evident that the hepatic venous pressure, 6 mm Hg is a little higher than normal That in general is because of an increase in intra abdominal pressure found in many cirrhotic subjects The wedge pressure is 21 mm Hg in contrast to the normal mean of 5 mm Hg and actually there is no overlap at all between the cirrhotic group and the normal group Normal subjects in our experience have gone up as high as 9 mm Hg and no cirrhotic subject has gotten down to that level Some of the cirrhotic subjects went up as high as 40 mm Hg

*Wilkins* Isn t that very good evidence for your thesis that there is no free communication between veins of the type in which the catheter is wedged because if there were there would not be such a great difference between hepatic vein pressure and this pressure in other words if there was a communication that would drop the pressure At least one can conclude that in the cirrhotic liver there are no communications between veins of that order

*Myers* That is quite right and that would be our interpretation of this high pressure The normal liver is a low resistance system with fairly rich small vessel anastomoses In liver disease there is interference with this rich small vessel anastomotic network and no sizable communications exist thereby there is a high resistance system and the pressure in the occluded area rises to these quite high levels Again I would point out that the blood in this system is not stagnant in that its oxygen concentration and glucose concentration are the same as in the free hepatic vein

The figure of 27 mm Hg for the portal vein is again the average of the surgical figures I could find in the literature and the arteriolar pressure is the same surmise as we showed before You will note then that the so-called sinusoidal pressure of 21 mm Hg is in general agreement with the portal venous pressure

*Green* What do you mean by an arteriolar pressure? Are you thinking of the pressure in the capillaries that the hepatic artery supplies?

*Myers* No the reason I put it this way is that I presume the hepatic arterial radicals have the same resistance at the arteriolar level as other arteries and therefore it is proper to speak of an arteriolar pressure here

*Green* Where is this pressure drop of 30 mm Hg down to 6 mm Hg that you showed in the previous figure?

*Myers* I think that occurs in the liver between the arteriole and the sinusoid in this low resistance setup

*Green* There must be some very constricted vessel because the pressure dropped

*Myers* No I do not think so other than the arteriole itself I again

ably due to lack of oxygen, but I am not a bit repentant about raising this question, because now I have learned that a great many people are competent on the subject The only measurements that I know of, that have been made in the last few years, of the liver blood flow in shock seemed to show that although flow decreases it does not decrease nearly as critically as, for example, the blood flow of the kidney and possibly of many other organs and tissues This assumption of the last few years that the liver was the critical place, because it suffered critically from oxygen lack, seemed to me to be rather uncertain I wanted evidence for this belief

*Myers* Figure 50 is a schema of what one finds in portal cirrhosis of the liver, again with the catheter wedged in a small hepatic venous radical If we again work backward from the hepatic venous system, it

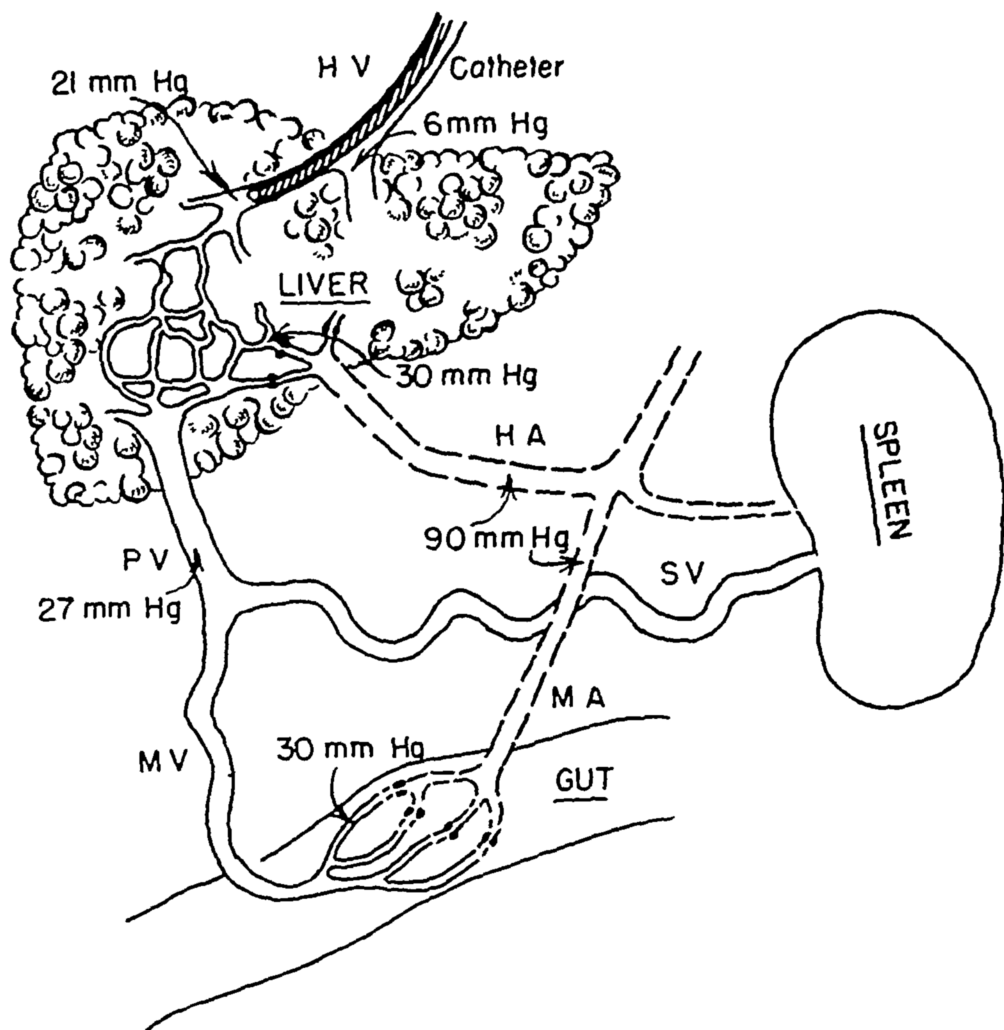



FIGURE 50 Schema of the hepatic circulation in cirrhosis with portal hypertension

trolled for considerable periods of time Later the artery may dilate readjusting the proportion of arterial to portal blood entering that part of the lobule or the portal vein may dilate or the artery may contract The above phenomena have been recorded in motion pictures taken of frog liver lobule and some of them have since been observed in the livers of rhesus monkeys

The ordinary textbooks of physiology have not kept up with the literature available on this problem The textbooks usually quote R Burton Opitz to the effect that from one fourth to one third of the blood entering the liver is arterial Soskin Essex Herrick and Mann (37) found in dogs that sometimes as much as 90 per cent of the blood flowing through the liver enters by way of the artery and but 10 per cent by way of the portal vein Further physiological readjustments sometimes shifted the proportions to the point where but 10 per cent of the blood entering the liver passed in by the artery the other 90 per cent entering by the portal vein

Investigators proposing to interpret the results of cannulization experiments should face the fact that the points of junction of the hepatic artery and portal vein at the periphery of the lobule have a specific anatomy make definite connections and that the tonus of these small vessels continuously maintains very precise control of the kinds and ratios of blood entering the lobule

This is the point I was trying to arrive at As you described it, the major resistance that regulates the extent to which the hepatic artery affects the sinusoidal pressure may well be in the terminal part of the hepatic arteriole

*Green* But if you are going to assign a pressure shouldn t it be at some anatomically discrete point just upstream or downstream from some constrictor tissue? If you want to assign a pressure I imagine the pressure drops more or less rapidly as the blood flows from the hepatic artery along the arteriole to the sinusoid and then levels out at about 7 mm Hg in the liver sinusoids

*Nickerson* It seems to me that this is a very convenient way of putting it, because I am sure there is a point where the pressure is precisely 30 mm Hg

*Green* Yes but does that point have any physiological significance?

*Baez* Dr Knisely from your past description of it in frogs and monkeys I gathered that the sinusoid has two incoming vessels one from branches of the hepatic artery and the other of portal origin, each of which is provided with a sphincter like arrangement capable of opening and closing independently of the other one If this is correct then

compare this system to what you find in the pulmonary circuit when a high-pressure patent *ductus* comes in

*Green.* The 30 mm Hg would seem to be a little bit of an artificial assumption

*Myers* As I say, it is entirely a surmise that there exists a pressure gradient of from 30 mm Hg in the arteriole to about 5 mm Hg in the sinusoid of the normal liver, and to about 21 mm Hg in the sinusoid of the cirrhotic liver

*Nickerson:* Is it not reasonable to assume that the major resistance is in the terminal portion of the arteriole and that the pressure of 30 is really the pressure a few millimeters back from where it empties into the sinusoid?

*Green* It is rather artificial to assume some pressure halfway down the arteriole I do not think it would have any physiologic significance

*M Knisely* At this point in the consideration of these problems, it seems necessary to point out that the precise anatomy where the hepatic artery and portal vein join each other at the periphery of the liver lobule and the different physiological behaviors of the anatomical parts must be considered when trying to interpret pressure measurements made by cannulizating the artery and/or the portal vein

We published the anatomy and behavior of the parts as directly observed through the microscope in the livers of frogs and rhesus monkeys (19) You may also see Cowdry's work (36) The hepatic artery runs along the portal vein somewhat like a vine on a tree The artery gives off a side branch, "the arterial sinus twig," which attaches to a hepatic sinusoid usually about one fourth up to one third of the distance from the periphery of the lobule toward the center There are large arterioportal anastomoses which connect the sides of the hepatic artery to the sides of the tips of the portal vein When these are open, they run arterial blood into the side of the portal vein and directly distribute arterial blood through many or all of the tips of the portal vein peripheral to the arterioportal anastomosis

Consider the hepatic artery and portal vein running together up the side of one liver lobule The hepatic artery sometimes is contracted tightly shut and the portal vein wide open in which case pure portal blood only passes into the sinusoids of the liver lobule Contrariwise, the portal vein is sometimes tightly shut and the hepatic artery widely dilated pouring highly oxygenated arterial blood at high pressure in torrents through the sinusoids of that portion of the lobule Further, at other times the hepatic artery and the portal vein are partly dilated and the rate of flow through each is thereby precisely controlled, the proportion of arterial and portal blood poured into the lobule is con-

the portal venous radicals out near the spleen mesentery and so forth there is a perfectly normal wedge pressure with a low resistance hepatic circulation in the absence of significant cirrhosis

*Green* In your previous diagram you showed I believe a pressure drop from 30 mm Hg in the mesenteric capillary to 7 mm Hg in the portal sinusoids—in other words a pressure drop of about 22 mm Hg In these last two figures you have suddenly lowered that pressure drop from mesenteric capillaries to portal vein or portal vein to sinusoids down to 2 or 3 mm Hg Shouldn t you maintain about the same pressure drop and thereby have to raise your mesenteric capillary pressure up to perhaps 50 mm Hg to indicate that there is a rise in intestinal capillary pressure? I believe it does actually occur doesn t it with this type of obstruction?

*Myers* Certainly the capillaries in the gut will be full I do not really know whether the gradient is tremendously different from normal or not

I must repeat that 30 mm Hg is entirely arbitrary and has no great meaning I have no brief for it The 28 mm Hg is the surgical figure again in individuals who have been operated upon and who actually had their portal venous pressures measured

*Green* This would assume a flow reduced to about one tenth of the previous flow and I do not believe it would drop that much

*Selkurt* We have studied the influence of elevating portal pressure on mesenteric blood flow in dogs With restrictions to outflow great enough to raise portal pressure to 30 to 35 cm saline flow in the mesenteric bed is reduced to about one half of the control level These are acute experiments What it would do in chronic experiments I do not know

*Myers* Let us continue then, with Table XII which will show a very limited experience with these pressures in individuals who have been operated on for portal hypertension The first two patients had end-to-side portacaval anastomosis so that the portal venous blood was completely diverted from the liver In the usual cirrhotic patient the sinusoidal pressure and the portal venous pressure are in reasonable agreement, as Dr Wood commented a moment ago Here where the portal venous blood is completely diverted from the liver there is no significant effect on the hepatic sinusoidal pressure W D s pressure preoperatively was 25 mm Hg the actual pressure at operation was 26 mm. Hg and the pressure taken sometime postoperatively after 2 to 4 months was 22 mm Hg and the gradients on the right hand side of the table, did not change significantly Likewise in patient H H the pressure preoperatively was 17 mm Hg at operation 30 mm Hg

the pressure in the sinusoid must be continually changing as a reflection of sphincter action

*M. Knisely:* I am sure there is a great deal of variability there

*Baez:* Have you actually measured the pressure in the sinusoid?

*M. Knisely:* The measurement of it requires tools, time, and patience, that is all I do not say this in any way disagreeing with you But there is no conflict here

*Myers:* There is, in the cirrhotic liver, a very high resistance system and a marked gradient between the wedge pressure and the hepatic venous pressure which clinically actually is diagnostic of this situation

Although Figure 51 does not apply too much to what we are discussing, it shows, in the portal vein at the darker line, an extrahepatic constriction which gives portal hypertension from a variety of causes, and it also shows that the intrahepatic circulation is normal Therefore, in extrahepatic portal hypertension, where the pressure is quite raised in

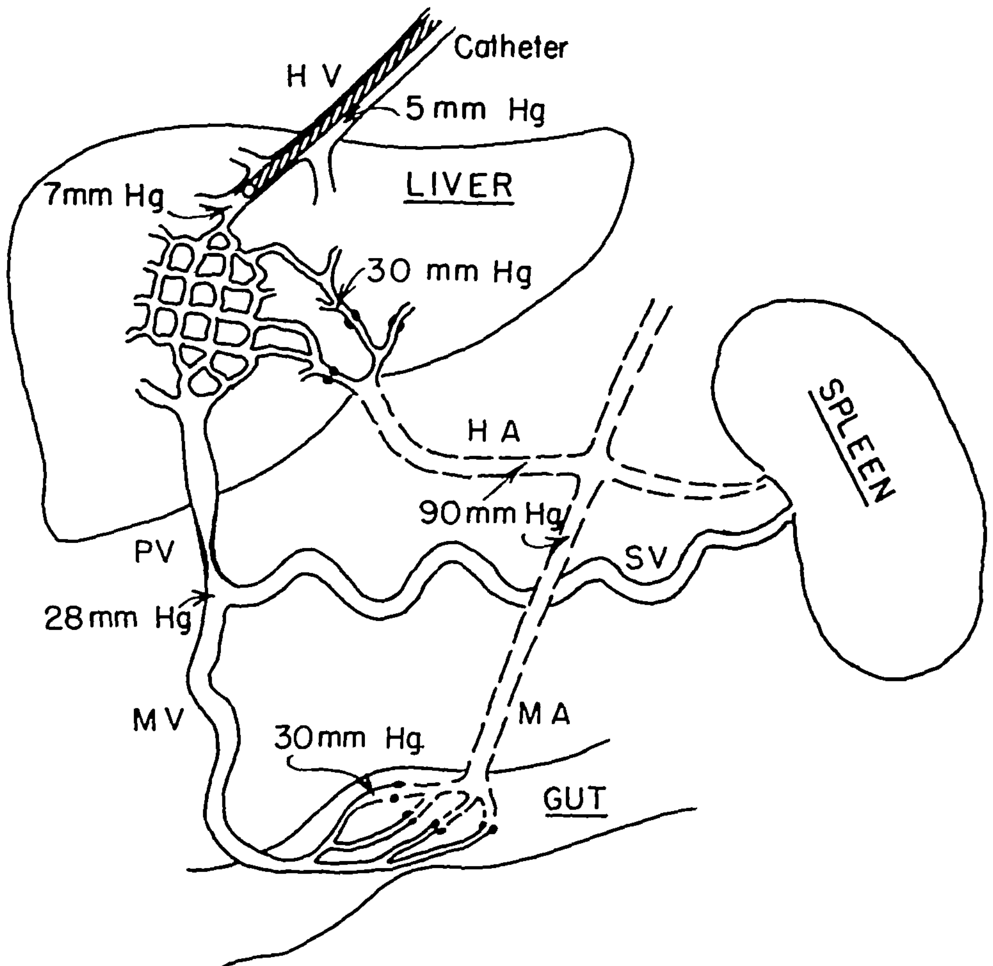



FIGURE 51 Schema of the hepatic circulation in extrahepatic portal hypertension

*Bradley* Do you think it is possible that the arterial inflow actually increased after the portal vein shunting operation?

*Myers* I think it is entirely possible It probably was as I intimated much higher than the normal hepatic arterial inflow before operation This would be in accord with the surgical observations at operation—that the hepatic artery in these cirrhotic patients is dilated and there is a thrill over it It is possible that the portal venous inflow was appreciable before operation and that after operation the hepatic arterial flow rose so as to compensate for it and thereby the pressures remained the same I do not know any way to settle that point on the basis of the information at hand

*Stead* You do not have to say it did if you do not wish to because you could say that when sinusoidal pressure reached a certain level the obstruction to portal flow also reached a certain level and everything flowed off through collaterals Therefore, there really was practically no portal venous flow before you tied the portal vein Either would certainly be possible

*Green* Did you happen to record the acute effect of tying off the portal vein during the operation?

*Myers* No we have not done that

*Green* That would be a rather good answer to your question, wouldn t it?

*Myers* Actually I think Dr Reynolds* (38) in Los Angeles made some such observations but I do not remember any striking changes at the time of operation Do you recall that any better than I do Dr Bradley?

*Bradley* No I do not Most of the patients we studied (39) showed a definite decrease in blood flow postoperatively

Do you think that diversion of portal inflow could be compensated for by vasodilation?

*Selkurt* Sancetta (40) has done some work on that Portal ligation was followed by an immediate increase in hepatic arterial flow

*Bradley* Vasodilation need not be postulated to explain increased arterial inflow It could be an automatic consequence of the arrangement of resistances

*Green* There would have to be a decrease in the hepatic artery resistance if the flow goes up because there was no change in pressure in the portal sinusoid

*Selkurt* If one considers that the portal radicles and arterial channels lie parallel in the liver cutting off the portal supply would decrease

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*Reynolds paper does not provide the data in question

TABLE XII

Occluded Hepatic Venous Pressures in Three Patients Undergoing Operation for Portal Hypertension Secondary to Cirrhosis of the Liver

| Pt | Operation | "HS" | HV | Gradient |
|---|---|---|---|---|
| W D | Portacaval, end to side | a 25<br>op 26<br>p 22 | 4 5<br><br>6 | 20 5<br><br>16 |
| H H | Portacaval, end to side | a 17<br>op 30<br>p 22 | 10<br><br>9 | 7<br><br>13 |
| M B | HA ligation | a 20<br>op 30<br>p 14 5 | 9 5<br><br>3 | 10 5<br><br>11 5 |

and after operation 22 mm Hg He had some hepatic decompensation with jaundice after operation, which may account for the fact that the gradient actually went up a bit

In neither of these patients did the hepatic blood flow as estimated by the BSP technic go down significantly as the result of the diversion of the portal venous blood, and one might surmise, then, that actually in these individuals before operation there was very little portal venous contribution to the total hepatic blood flow, therefore, diverting it had little effect on pressure relationships in the liver, as studied by this technic One might also say that this would help explain why complete diversion of the portal venous blood has no great deleterious effect on hepatic function in these individuals with cirrhosis In these two cases, the sinusoidal pressure obviously is entirely unrelated to portal venous pressure

In the last patient, who had an hepatic arterial ligation, the hepatic venous pressure was high on the initial measurement, and there was no significant change in "sinusoidal" pressure as a result of the operation, the gradient therefore remained the same The after-operation study was done 2 months postoperatively, and it is perfectly possible that by this time collaterals had re-established an adequate arterial blood supply to the liver

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the pressure and volumetric encroachment on terminals of the hepatic artery This might permit more flow through the hepatic artery, this, however, is just a speculation

*Bradley* Isn't it a fairly simple situation? If the inflow from the portal system is reduced without change in the resistances distal to the sinusoids, the arterial inflow will automatically increase, because with the fall in portal inflow the pressure within the sinusoids must drop temporarily

*Green* Except you did not show any drop in your sinusoidal pressure

*Bradley* No, but the sinusoidal pressure would be quickly restored by the corrective expansion of arterial inflow

*Myers* We were not there at the right time to obtain data on what Dr Bradley would like to know

*Bradley* One may postulate a momentary drop in sinusoidal pressure and then a restitution Of course, this should be demonstrable in some change in the A-V oxygen difference, because in this situation a larger quantity of oxygen would be brought into the liver in the same volume of blood The blood replacing the diverted portal blood would be higher in oxygen content

*Myers* Yes, if the portal vein had made a really sizable contribution In these two individuals (W D and H H), there was a slight rise in hepatic A-V oxygen difference between the preoperative and postoperative measurements

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logic conditions there are variations and differences in the stroke volume of both ventricles

Blood pressures in the pulmonary circulation are very much lower than in the systemic The mean blood pressure in the pulmonary artery is about one seventh to one tenth of the mean pressure in the aorta and the left atrial blood pressure is slightly higher than the right atrial pressure

The volume of blood in the pulmonary circulation estimated very grossly is one fifth to one tenth of that in the systemic circulation This will be discussed later in more detail Estimates vary from 500 to 1 000 ml Since temporary heterodynamism of both ventricles prevails this volume will vary continuously It will also do so during cyclic phases of respiration

In addition there are some differences in the behavior of both circulations under conditions of stress such as exercise Until recently the pressures in the pulmonary circulation were said not to increase during an exercise which would result in a nearly three fold increase of the basal flow In the systemic circulation there is always some increase, but the over all systemic resistance drops in very severe exercise to about one half of the basal value whereas resistance in the pulmonary circulation drops to about one third of the basal value

I must acknowledge that in our studies of the effect of exercise on the pulmonary circulation, pressures were measured after the subject had reached a steady state i e when the circulation and respiration as judged from various measurements including ventilation oxygen uptake respiratory exchange ratio pulse rate and blood flow have ceased varying significantly However in a paper sent to me for review and comment, I was confronted with good evidence that immediately after the beginning of even a mild exercise there is in the pulmonary artery a mean pressure rise which amounts to 4 to 5 mm Hg We have been able to confirm this finding and to confirm further that the pressure rise is maintained for a short period of time and that as a rule as the exercise is continued the pressure tends to return to the control level so much so that when a steady state is reached it is as we found in our previous studies

Such a course of events is rather to be expected Dr William F Hamilton always prodded me about the necessity of an initial pressure rise in order to open up some closed vessels which may accommodate a large flow increase during exercise The above mentioned observations provide the answer

Another important distinction between both circulations results from the course of large pulmonary vessels in contiguity with structures like

# THE PULMONARY CIRCULATION*

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STUDIES OF THE pulmonary circulation date back to the 1880's, and, in spite of a considerable number of publications, there is still little agreement about some of the most fundamental problems For instance, it is still not known whether the vasomotor system plays an active role in the control and regulation of the pulmonary circulation The classical reviews of Tigerstedt (1) and of Wiggers (2), published respectively in 1903 and 1921, give the impression that after taking into account all the evidence, they were not sufficiently convinced so that they could take a strong stand one way or another concerning the role of the vasomotor system On the other hand, in a more limited review published recently by Lilienthal and Riley (3), these essayists took a very strong stand in favor of its role Perhaps this problem will be solved in the course of the discussion here

## COMPARISON OF CERTAIN FUNDAMENTAL ASPECTS OF PULMONARY AND SYSTEMIC CIRCULATIONS

In an equilibrium state, the mean blood flow through the pulmonary circulation is identical to the mean blood flow through the entire systemic circulation

In some interesting studies of the functional anatomy of the ventricular contraction, Dr Rushmer (4) has recently contrasted the geometric configuration of the cavity of both ventricles the right, hemispheric, is best adapted to the transfer of a large volume of blood into a low-resistance system, whereas the left, cylindric, is best adapted to eject blood against varying resistances

We do not know whether what I stated about equal mean flow applies to a beat-by-beat analysis, it is very likely that even under normal physio-

*The work reported here was supported by a research grant (P H S Grant H 833 (C)) from the National Heart Institute of the National Institutes of Health U S Public Health Service

sarily limited the error you were permitted to expect Would you repeat that here to keep our thoughs straight?

*Burton* If you like I would agree with Dr Cournand that Visscher in the original paper (6) raised a very important principle but I think his final diagram is at fault in estimating how very great the error can be, in that he assumes that there is no connection between these two things—the A V difference and the flow After all these must be related to the metabolism There may be a phase difference in the swinging and I understand although I have not read this but only heard it in our previous discussion that this has been taken into account more correctly since then I think that Visscher s original estimate of how wrong one could be is greatly exaggerated because of his ignoring the fact that there is this connection that the product of these two things must be equal to something which is relatively constant

*Cournand* In the derivation of the formula the oxygen uptake is eliminated completely

*Burton* Yes so that while the principle is a very valuable one and it has done a very valuable thing for us in making us aware of this difficulty his assessment of how great the error can be is greatly exaggerated

*Cournand* He did not say that this would necessarily be the error but he intimated how great the error could be When he measured flow in the acute anoxic state he found that the flow by the dye method increased significantly whereas by the Fick method the calculated flow did not increase Of course Dr Wood could probably tell us that the same error based on differences in phase in the time-concentration and volume-concentration curves which occurs during sampling might also be very significant in the dye method

*Wood* I would take a little exception to Dr Burton s statement concerning the paper by Johnson and Visscher in that the error that they postulated was correct under one set of assumptions namely that the phase relationship between the phasic variations in flow and the phasic variations in oxygen concentration was such that the error would be a maximum

The only thing omitted was what the phase relationship was If there are phasic variations in flow and oxygen concentration the actual error that occurs is due to the difference between a time average and a volume average sample This difference is related to the product of the amplitude (the peak to-peak amplitude) of the variations in oxygen content and the peak to-peak amplitude in the variations in flow times the cosine of the phase angle between these variations (7) Since the cosine of an angle of zero degrees is 1 and of 180 degrees is 1 if the

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*Burton* Yes so that while the principle is a very valuable one and it has done a very valuable thing for us in making us aware of this difficulty his assessment of how great the error can be is greatly exag gerated

*Cournand* He did not say that this would necessarily be the error but he intimated how great the error could be When he measured flow in the acute anoxic state he found that the flow by the dye method increased significantly whereas by the Fick method the calculated flow did not increase Of course Dr Wood could probably tell us that the same error based on differences in phase in the time-concentration and volume-concentration curves which occurs during sampling might also be very significant in the dye method

*Wood* I would take a little exception to Dr Burton s statement con cerning the paper by Johnson and Visscher in that the error that they postulated was correct under one set of assumptions namely that the phase relationship between the phasic variations in flow and the phasic variations in oxygen concentration was such that the error would be a maximum

The only thing omitted was what the phase relationship was If there are phasic variations in flow and oxygen concentration the actual error that occurs is due to the difference between a time average and a volume average sample This difference is related to the product of the amplitude (the peak to-peak amplitude) of the variations in oxygen content and the peak to-peak amplitude in the variations in flow times the cosine of the phase angle between these variations (7) Since the cosine of an angle of zero degrees is 1 and of 180 degrees is 1 if the

two variations are at that phase angle, the error will be at a maximum, but since the cosine of 90 degrees is zero, if they are 90 degrees out of phase there will be no error in spite of the fact that there may be big fluctuations in flow and oxygen concentration That is the only error if it can be called such and, if so, it is only an error of omission in the Visscher-Johnson paper

*Burton* I would accept Dr Wood's interpretation, except that I think it is almost impossible that the phase can be 180 degrees Wouldn't you think so?

*Wood* I don't know about that If the flow was 180° out of phase with the concentration That would mean that the flows were greatest when the A-V difference was least Is that right? I have to draw a picture before I can be certain that I am stating these phase relationships correctly

*Burton* I am thinking of the electrical analogy This would be a flow that had no resistance and nothing but the inductance resisting the flow, which would correspond to a vascular bed having no resistance at all but having tremendous elastic properties, which probably is so, isn't it?

*Wood* I think in actual fact what will be found is that the content of oxygen in the arterial blood is relatively constant, except perhaps during anoxia, and that the major phasic variations in blood oxygen content which occur in the intact animal occur in the mixed venous blood I think the phase relationships between oxygen concentration and flow can be almost anything because I believe that they are related to variations in the rate at which blood returns to the heart from areas with large differences in oxygen saturation of venous blood For instance, phasic variations in the return of relatively highly saturated blood from the renal veins and the more desaturated blood from the cavas (8) These phasic variations in venous return and mixing of blood from different areas and organs are associated with the respiratory cycle and just what their phase relationships will be in respect to possible variations in flow, I do not know (9)

*Cournand* Am I correct in saying that you have studied the variations in the mixed venous blood oxygen concentration and you found they were minimal, so that the error would be approximately 4 or 5 per cent?

*Wood* Yes, that is correct In intact humans we have studied, by several different technics, the possibility of phasic variations in oxygen content of mixed venous blood and have been able to detect such variations almost uniformly in normal subjects These variations are of

maximum amplitude in the inferior vena cava and it is estimated that they can be as large as from 10 to 20 per cent (8)

After passage through the right atrium and ventricle to the pulmonary artery these variations are much smaller Accurate estimations are difficult because of attenuation of the phasic variations under study by the recording system used This consists of a long cardiac catheter and a continuously recording cuvette oximeter In spite of the fact that the blood is withdrawn at a high rate of flow the dynamic response of the system is such that a good deal of attenuation of fluctuations with the respiratory cycle occurs (9) What one is forced to do until better methods are devised—and I am at a loss to know just how it can be done—is to study the dynamic response of the catheter-cuvette oximeter system to variations in oxygen saturation produced outside the body and thus determine how the system responds This information can then be used to predict back from the results in the actual experiment as to what the variations must have been in the pulmonary artery to produce the variations recorded by the cuvette-oximeter system

These variations at rest are very small and even if one assumes the maximum variations in flow they would not produce errors in the conventional application of the Fick method which would be over 5 per cent During exercise however these variations frequently become much bigger and may perhaps be as high as a peak to-peak amplitude of 20 per cent with each respiratory cycle Such variations could result in real systematic errors in determinations of flow by the usual Fick method if there were simultaneous variations in flow of large magnitude during the respiratory cycle and if these flow variations were in the right phase relationship to the variations in oxygen saturation

We cannot say whether there are errors or not but we can say that the possibility for significant systematic errors certainly exists It will be impossible to find out whether such errors do occur until one can define completely what the flow characteristics are in the pulmonary artery If the flow in the pulmonary artery could be measured from instant to instant and its phase relationships to the variations in oxygen content were known then the error in determination of flow by the conventional application of the Fick method could be calculated (9)

*Cournand* You see what Visscher and Johnson have started Even if the magnitude of error that they imply does not necessarily apply under special sets of circumstances they have at least called our attention to a new physiologic problem i e the cyclic variations of flow through vessels and particularly the pulmonary arteries

In an article written in 1947 (10) concerning the effect of acute anoxia upon the pulmonary artery pressures we described how we

measured blood flow by the Fick method, and like Visscher and his collaborators, we calculated that under such a state, the pulmonary blood flow did not increase However, Rahn and Otis (11) demonstrated to our satisfaction that during acute anoxia, the oxygen uptake by the lung does not really decrease, as we had found, and this apparent decrease is related to the duration of the unsteady state of gas equilibrium through the lung, the blood, and the tissues It may take more than 20 minutes for a new steady state to be reached and therefore the Fick principle cannot be applied, short of that time

To emphasize this point it is not correct to use the difference between inspired and expired $O_2$ in the lungs to determine the $O_2$ uptake by the lung capillaries, under all circumstances A steady state must be attained and the best means to establish that such a state has been reached is to determine the respiratory exchange ratio (respiratory quotient) of the lungs It is only when this figure corresponds to a reasonable figure for the respiratory exchange ratios in the tissue that a condition of steady state of gas exchanges may be presumed to exist

Nahas and Visscher et al (12), working on the effect of acute anoxia in the dog, give data indicating that, with respiratory exchange ratios of the order of 3, the calculated $O_2$ intake is about one half of that calculated during the control period Obviously you cannot use such data to measure blood flow by the Fick principle

We are at the present time engaged in a comparative study of the dye and direct Fick methods in man during acute anoxia and we are endeavoring to determine under what conditions the Fick method may be used

### PULMONARY ARTERY WEDGE PRESSURE—"PC" PRESSURE

With regard to the validity of the methods to measure blood pressures in the pulmonary circulation, caution should be exercised when a catheter is used The pressure contours obtained are oftentimes greatly deformed by artifacts, which are mostly caused by the whipping of the catheter within the heart Varying degrees of damping and simultaneous recording of pressure within the ventricle may help to obtain fairly accurate systolic pressure values Many published values are worthless because extreme care has not been taken

You are probably all aware of the fact that Hellems and his collaborators (13) introduced catheters in the pulmonary artery as far as they would go and that the pressures thus recorded were presumed to be one of three things capillary, venous, or left atrial pressures Dr Burton has expressed his opinion about the significance of wedge pressures in the *Annual Review of Physiology* (14)

The use of quotation marks around PC pressures is a clear indication that after all these years what is measured even in the hands of the proponents of the method is not exactly defined In the present state of our knowledge the pressure measured after proper wedging of the pulmonary artery is probably best related to the left atrial pressure

*M Knisely* A moment ago you suggested that you might be measuring any one of about three or four things Now in any single case is there any way to know which one you are measuring or is there a whole collection of data each one measuring different things perhaps?

*Cournand* You are measuring the pressure which is obtained after wedging This is all you can say for certain Simultaneous determination of mean wedge and left atrial pressures have indicated that in the given experimental instances the two pressures were not significantly different Dr Wood has made such comparisons Others have made such comparisons on the basis of left atrial pressure records obtained by introducing a needle in the left atrium through a bronchoscope

One question arises—whether or not the pressure curves represent events in the left atrium Retrograde transmission time is seldom taken into account when left atrial and wedge pressures are recorded simultaneously One wonders whether the deflections on the record of wedge pressures are not due to heart impacts transmitted through the air and fluid *media* of the lung in a closed chest In any event Ankeney (15) has shown that with the open chest the only valid pressure tracings after a catheter has been introduced in a small artery and secured tightly with a ligature in place are those without any deflections Surprisingly enough, no study has been made of the state of the vessel walls beyond the point of wedging an interesting point since flow is supposed to cease within the vessel

There are a number of physical conditions which require further analysis before one knows exactly what happens after wedging a catheter in a pulmonary artery For practical purposes I am willing to admit that the wedge pressure is low when the left atrial pressure is low and is high when the left atrial pressure is high

*Burton* In watching one of these wedge catheters under fluoroscope is it possible to see the tip backing up?

*Cournand* No it is not supposed to move

*Burton* It is quite still?

*Cournand* It is still and the saline fluid flows at a rate of 5 to 10 drops per minute

*Burton* I was very impressed watching Machella (16) measure velocity in the pulmonary artery to see how very much movement across the body there is in this artery People using catheters know that if they

move a catheter outside the body large fluctuations appear on the recorder It is surprising to me that such people ignore this component of kinetic energy in movement of the catheter when it is in the vessel

*Cournand:* This criticism applies to the pressure taken in the pulmonary artery without wedging It is possible to see the catheter tip moving, and this probably is one of the important causes of artifacts in pressure tracings But this criticism does not apply to the wedged catheter

*Wood:* At the outset I also was very pessimistic about the significance of wedge pressures However, somewhat to my surprise, after doing a series of simultaneous determinations of wedge pressures and left atrial pressures in the operating room, I gradually came to think that this wedge pressure really does measure something which is related reasonably closely to left atrial pressure (17) When one makes such measurements simultaneously in the left atrium and in the pulmonary artery wedge position, there is a slight delay between the peak of pressure in the left atrium, at least in our experience, and the peak of pressure in the wedge catheter

Another point that should be kept in mind is that, in relation to wedge pressures, there is a difference between the dog and the human I have not done them myself but there has been in our laboratory quite a series of comparative studies of wedge and left atrial pressures in dogs Significant differences were frequently obtained between pulmonary artery wedge pressures and left atrial pressures in the dog * I don't believe that in the dog the same reliance can be placed on pulmonary artery wedge pressures as a measure of left atrial pressure as can be done under properly controlled circumstances in man

Findings in the dog are different in another respect It is extremely rare, in fact I can remember only one instance of a catheter wedged in a pulmonary artery in a dog from which a blood sample could be withdrawn In man, on the other hand, it is the exception rather than the rule not to be able to withdraw fully arterialized blood from the pulmonary artery wedge position (18)

I don't know just what the anatomic basis is for this difference between the human and the dog in relation to pulmonary wedge pressures but suspect that the two are not equivalent In our experience we would not subscribe to Ankeny's statement (19) that a wedge pressure cannot be accepted as such unless it is a flat line, i e , devoid of fluctuations Actually we use diametrically opposite criteria A good

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*Denton, C , Wakim, K G , and Essex, H E Comparison of left atrial and pulmonary artery wedge pressures in dogs (Unpublished data)

wedge pressure in our experience has a definite contour and is what one might call a freely recording pressure and not a flat line (17)

*Remington* Could the difference between the dog and human simply reflect the relation of catheter size to peripheral vessel diameter?

*Wood* You mean it would wedge in bigger vessels?

*Remington* Yes

*Wood* It is possible, although we obtain good wedge pressures from infants which are smaller than dogs

*W Knisely* What is the actual outside diameter of the catheter?

*Cournand* It is 1 mm

*W Knisely* Is that the smallest outside diameter? What is the smallest outside diameter used?

*Wood* The No 6F catheter which is most often used in our laboratory both in man and in the dog has an outside diameter of approximately 2 mm

*Nickerson* Would you say a word about the relationship of these wedge pressures to the absolute left atrial pressure?

*Cournand* What do you call absolute—the mean?

*Nickerson* The mean left atrial pressure

*Cournand* I have stated previously that the mean wedge pressure according to some is almost identical to the mean left atrial pressure

*Nickerson* What I was thinking of is this There is a difference in the transmission of the pulse wave with differences in the mean left atrial or pulmonary venous pressures and I wonder if some of the difference between human beings and dogs particularly the human beings at operation is that these usually have an elevated mean left atrial pressure whereas the dogs have a considerably lower pressure

*Wood* There is a paper by Haddy (20) and co-workers concerning a study of wedge pressures in the dog These workers are very pessimistic as to its value One of the statements made was that wedge pressures cannot be relied upon unless there is an elevated left atrial pressure In our experience still quite limited the left atrial and wedge pressures correspond well when measured simultaneously and when the former was not elevated however the similarity of contours under such conditions is not as consistent as it is in subjects with mitral stenosis and insufficiency but the agreement as stated above in mean pressure levels was excellent (17)

*Bing* We have been guilty of ascribing too much importance to the shape of the wedge pressure a thing which I am convinced was erroneous It seems that the only value of the wedge pressure is to give the approximate height of the pulmonary vein pressure

I am in doubt as to whether even the left atrial pressure permits a

differentiation between mitral stenosis and insufficiency. Mr. Allison* in Leeds, England, has taken direct left atrial pressure through a bronchial catheter. He kindly sent us some of his tracings; it is difficult using these tracings, to differentiate between stenosis and insufficiency.

Such a differentiation is important from a clinical viewpoint, I must admit, but if there is no difference in the pressure in the left atrium, how can we expect the wedge pressure to be of value in differentiating mitral stenosis and insufficiency?

*Cournand:* There was no difference in the pressure between the left atrium—

*Bing:* There was no difference between the pressure recorded in the left atrium in the presence of mitral stenosis and that recorded with insufficiency. There was absolutely no indication whether the patient had a mitral stenosis or insufficiency.

*Cournand:* In other words, the amplitude of the events on the tracings was not greater?

*Bing:* That is correct.

*Cournand:* I believe the pathologist could tell us something about changes occurring in the wall of the left atrium in the course of mitral stenosis. Depending upon the degree of muscular hypertrophy or upon the presence of laminated clots, the curves relating volume and pressure changes within the left atrium must be quite different.

*Bing:* What I mean is that we cannot base too much credence on the shape of the pulmonary wedge pressure if we cannot place any credence in the shape of the left atrial pressure in the first place.

*Cournand:* You don't believe that you record with any degree of accuracy left atrial pressure by introducing a needle in the left atrium with a suitable recording system?

*Bing.* I do not know, but Allison's tracings do not bear out some of the published data.

*Cournand:* Some of my associates are recording pressure curves in the operating room, but, since these records have not been analyzed yet, I would rather say nothing on this subject.

*Lamport:* The fact that the wedge pressure and the left atrial pressure are so close together is of importance. It simply demonstrates that there is a very low pressure gradient from this wedge spot into the left atrium and that must mean that the intervening vessels have a very large cross section so that the hindrance or resistance of those vessels to blood flow is extremely low.

*Wood:* I do not think it means that at all because it has been demon-

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*Personal communication.

strated that the flow is stopped in the small segment of lung supplied by the vessel in which the catheter is wedged (21) If there is no flow going through that vessel it is a static system and one cannot tell anything about resistance to flow through the vessels in question In a sense the vessels distal to the catheter apparently act as an extension of the catheter system leading to the pulmonary veins and left atrium If there is no flow or greatly reduced flow the pressures obtained cannot be used as any indication of resistance

*Lamport* Don t you feel there must be an anastomosis here which is very rich in the lung? Since you can obtain both red and cyanotic blood from his catheter under different conditions is not the catheter tip in a location which is certainly upstream from the left atrium? Does not the closeness of wedge pressure to that in the left atrium indicate that there is a low pressure gradient from the left atrium to the point of connection between static and flowing blood at the wedge? I understand what you mean about the catheter and the vessel in which it is wedged being a static tube but it must finally connect, like a static manometer attached to the wall of a pipe with a flowing system There is an infusion going into the catheter and the fluid is going out into the anastomosis of the wedged vessel you can withdraw blood

*Moe* In any event the flow into the system from collateral channels must be less than the flow which would normally exist were the catheter not in place The recorded pressure must therefore be less than normal and you cannot therefore assess the resistance beyond the catheter

*Lamport* If it is going all the way to the left atrium yes but how can it? You have a relatively small size catheter much smaller than the vein, so it must be true that your point of connection with the flowing blood is upstream from the atrium

*Moe* It must be on the upstream side of the atrium to be sure

*Lamport* Yes and the gradient to those points is very tiny I will admit I do not know exactly where the collateral connection is but it seems to me it must certainly be upstream.

Figure 52 shows an extremely formalized diagram of the pulmonary vascular system The circle shows where the catheter had wedged in a pulmonary artery and the pressure it reads is $P_w$ The pressure in other arteries this size (there are N altogether) is $P_A$ and that in the left atrium is $P_{LA}$ The shaded block represents the wedge normally supplied by the blocked artery If there were *no* anastomosis between any of the wedge and other pulmonary vessels in the manner shown in the figure the first connection between the vessels in the wedge and the flowing blood in the rest of the lung would be somewhere in the pulmonary venous system More precisely if the wedge is a random portion of the

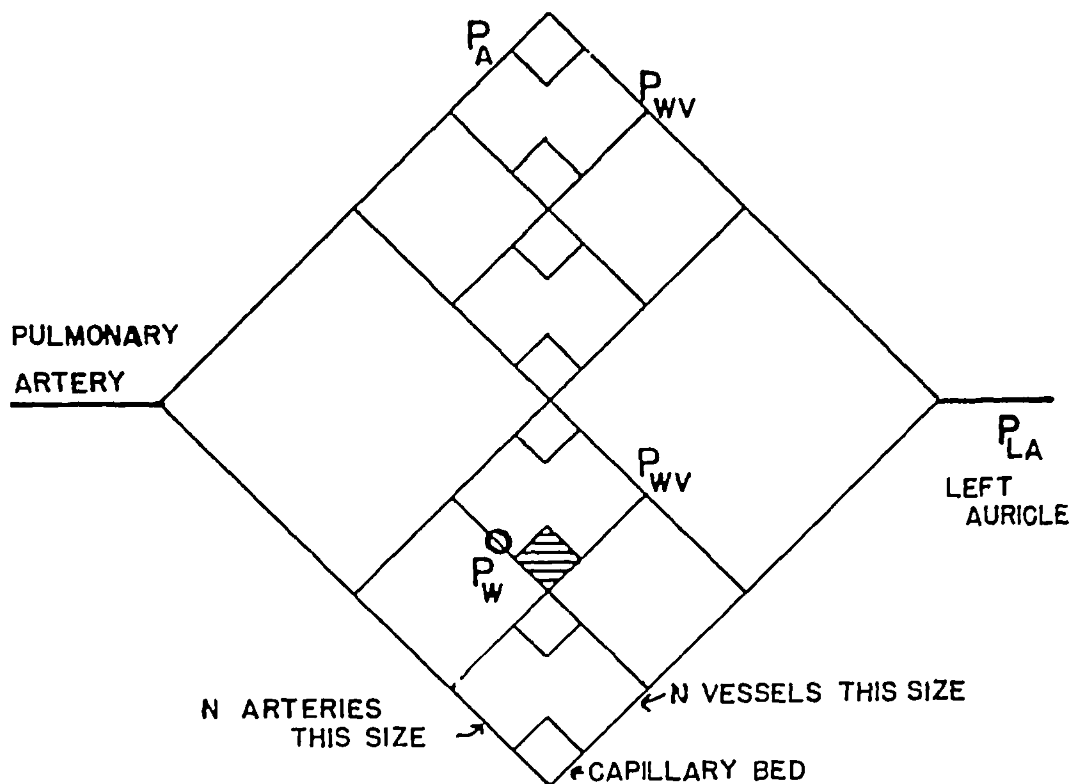



FIGURE 52 Highly schematized representation of pulmonary circulation, blood flow being always from left to right The letters *P* with various subscripts refer to blood pressure at the site at which they are placed and are described in the text $P_W$ represents the "wedge" pressure read from a catheter wedged in the artery indicated by a circle The square boxes indicate the capillary bed between arteries and veins, the hatched box being the one supplied by the wedged artery

lung bed, we can say that the connection between static and flowing blood cannot occur further downstream than the location at which the venous outflow of the wedge passes through a single vein to join with another vein actively draining blood from the rest of the lung

In the unwedged system,

$$P_A > P_{WV} > P_{LA}$$

In the wedged system (we omit consideration of the slight distortion of pressure at the venous confluence because of the change in flow resulting from wedging), assuming no anastomosis before the confluence at $P_{WV}$, the pressure read must be that at $P_{WV}$, since there is no flow and so pressure throughout is everywhere the same (Pascal's Law)

$$P_W = P_{WV}, \text{ when there is no anastomosis}$$

Or, $P_A > P_W > P_{LA}$

If there is anastomosis, the effect will be to shift upstream toward $P_A$ the pressure read at $P_W$ to the point at which anastomosis becomes effective Certainly anastomosis must be effective at the capillary level, so that we can expect that wedge pressure will lie somewhere between

Pv and pulmonary capillary pressure, depending on the actual level of effective collaterals

*Cournand* May I make this statement about pressures? When one measures pressure in the normal circulation the mean pressure in the pulmonary artery is of the order of 10 to 12 mm Hg the mean in the left atrium is of the order of 4 to 5 mm Hg The pressure one can record is between those two The error in reading a succession of tracings is as much as 3 or 4 mm Hg There is a very small pressure drop so I think the only interesting measurements that can be made are those that are found in mitral stenosis when the pressure gradient between the two is really significant

May I say also that in the very first paper on wedge pressures obtained from dogs by Dexter s group (22) the pulmonary venous pressure was on an average somewhat higher than the wedge pressure which shows the margin of error within which one operates

One more interesting fact is that after passing a catheter through an interatrial septal defect and wedging it into a pulmonary vein the pressure recorded has been found to be identical to that of the mean pulmonary artery pressure (23) On the basis of these observations it would appear that the pulmonary capillary pressure must be higher than the left atrial pressure

*Wood* We have made similar studies in approximately fifteen patients and the observation you report is essentially true (24) In patients with a low pulmonary vascular resistance and normal pulmonary artery pressure, mean pressures recorded from a catheter wedged in a pulmonary vein are similar to the mean pressure in the pulmonary artery and in some instances show contours which are similar to the pulmonary artery pressure pulse

However if the catheter is wedged in a pulmonary vein in patients with pulmonary hypertension—and we have done it in quite a number of instances—the mean pulmonary vein wedge pressure is quite different from mean pulmonary artery pressure It is higher than pulmonary vein pressure but it is much lower than pulmonary artery pressure Therefore the statement that has been made that one can use pulmonary vein wedge pressure as a measure of pulmonary artery pressure only applies I believe in cases in which the pulmonary artery pressure is normal We have good evidence to support this (24)

*Cournand* I used these studies as evidence that you may in unusual situations measure the pulmonary capillary pressure and what you just stated indicates that even this statement is not always correct

*W Knisely* Were there septal defects in the first fifteen you mentioned?

*Wood:* There are septal defects in all these cases, otherwise, you cannot make the measurement

*W. Kinsely:* They were not "intact" humans, then

*Wood* Well that is a matter of definition. These were patients with congenital, naturally occurring, septal defects

*Burton:* Doesn't all this suggest to us that we have a profound area of ignorance? I feel there is not much use in using hemodynamic arguments when we do not really know how many anastomoses there are between the capillary systems that are feeding different veins, or are fed from different small arteries After all, we look at the vasculature and we say it is like a network, but it may be that it has a sort of lobular structure so that the network we look at all drains into one little vein This last observation you made would suggest that if you obtain a pressure from a pulmonary vein wedge catheter, you obtain something about equal to that at the other, arterial, end It suggests that in that particular case there cannot be much intercommunication with other capillary systems, doesn't it? It seems to me until we have this intimate knowledge of the architecture, which I do not know that we now have, we cannot really argue very sensibly on hemodynamics

*Cournand* I agree with you

*M Kinsely* Oscar Batson has a motion picture of a special type of dissection of the lung of freshly dead pig which shows that the lung separates very easily into portions roughly the size of a walnut or a little larger The first implication of this study was that these were supplied by primary units of artery, vein, and bronchus There was also the indication that this kind of dissection could be done in the human being Thus far my only information is that Batson has the technic and he should be supported strongly while he prosecutes that research

*Cournand* I have not thrown into the discussion the fact that there are anastomoses between the pulmonary system and the bronchial system This must eventually further complicate pressures recorded indirectly

In summary, one should be very careful in interpreting wedge pressures and in introducing the data procured by this measurement into more or less complicated formulas from which to derive hemodynamic information

*W Kinsely* Dr Cournand, why is it necessary to wedge the catheter?

*Cournand* If you do not wedge, you will record a damped pulmonary artery pressure, if you wedge, then you record a pressure at some point distal to the wedging

*Green* Dr Bing stated, I believe, that you could not distinguish mitral

stenosis from insufficiency Would you care to commit yourself on that point from measurements either of wedge pressure or of atrial pressure recorded directly?

*Cournand* The only answer I can give is that Lars Werko a former collaborator of mine believes that he can make a diagnosis of mitral insufficiency on the basis of changes in the normal contours of wedge pressure records

There is much conflict in the literature as to the interpretation of these contours so that my answer is quite negative Would Dr Wood agree with this estimation?

*Wood* I agree with that I think the end of the story has not been reached yet but at the present time I do not think there is any ironclad way of diagnosing mitral insufficiency or distinguishing mitral insufficiency from stenosis by means of wedge pressures The relationship between the amplitude of the V wave and the level of the mean wedge pressure offers the greatest promise of real usefulness in this respect (25)

*Cournand* What is obtained directly in the operating room by needle puncture, or with small catheters is of great value since the pressure tracings make it possible to recognize mitral regurgitation

PULMONARY BLOOD VOLUME

The method used to measure pulmonary blood volume is based on Hamilton s principle (26) A dye is injected into the pulmonary artery and from the mean circulation time up to the brachial artery the point of sampling and from the cardiac output figure the total volume of blood between these two points may be estimated The volume measured includes the volume within the left heart The volume thus measured in normal man is about one fifth of the total blood volume or approximately 1 000 ml This is larger than what was expected from direct measurements made in dogs Surprisingly enough it has been reported that the central blood volume is not increased in mitral stenosis with considerable block

*M Knisely* Sjöstrand (26) wrote a book proposing very strongly that the lung was a reservoir and there was control of the amount of blood in it and of the amount of blood released from it

*Cournand* The Sjöstrand (27) idea had little success in Sweden where it originated As I remember there was some artifact in the preparation Anyhow blood was supposed to be pooled in special sinusoidal formations The lung might however play a role as a reservoir affected by ventilation There is little doubt about that but whether large amounts of blood are sequestrated is doubtful

*Wood.* There are septal defects in all these cases, otherwise, you cannot make the measurement.

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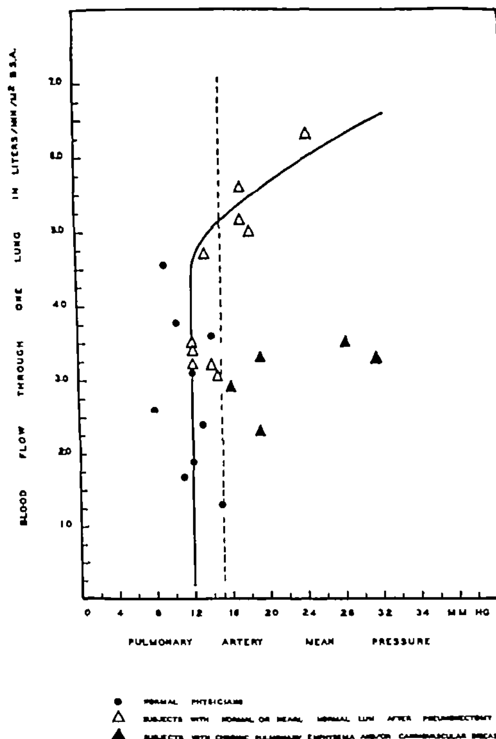



FIGURE 53 Relationship between blood flow through one lung and pulmonary artery pressure Reprinted, by permission, from Cournand, A Riley R L. Himmelstein A and Austrian R Pulmonary circulation and alveolar ventilation perfusion relationships after pneumonectomy *J Thoracic Surg* 19 *80 (1950)*

Dr Hamilton does not believe that the lung is a reservoir, but he does conclude that the heart plays such a role, and that whatever change there is in the central blood volume is due to changes in heart volume rather than pulmonary blood volume Is that correct, Dr Remington?

*Remington:* That is correct

*Nickerson* Would you care to comment upon changes in pulmonary blood volume in chronic mitral stenosis and acute left ventricular failure?

*Cournand* The data of Borden, Ebert, and their associates (26) indicate that there was a greater pulmonary blood volume change in left ventricular failure than in mitral stenosis, but as I stated, the method used may be questioned It is rather surprising that there should be no increase in pulmonary blood volume in the face of striking evidence of lung congestion

*Nickerson* The reason I asked is that in animals, particularly in situations such as the production of acute pulmonary edema produced in the rabbit by administration of epinephrine, it is very convenient to assume that the much greater response to the epinephrine of the systemic as compared to the pulmonary vessels leads to acute left ventricular insufficiency with an increase in pulmonary volume Do you feel that this is a legitimate explanation?

*Cournand* I think we might later go into the question concerning the effect of epinephrine upon the pulmonary circulation, but now I should like to show that there is some relationship between flow and pressure in the pulmonary circulation Our ignorance with regard to pressure-volume relationships of pulmonary vessels is appalling Only one group of physiologists, Sarnoff's, has attempted to establish in intact dogs the relationships between volume and pressure in the lungs (28) They measured increments in pressures in the pulmonary artery and left atrium as known volumes of blood were added The curve was similar to that obtained in an isolated pulmonary artery However, at any given volume, a higher pressure was obtained during addition than during withdrawal of fluid This difference they ascribed to change in elastic properties of the vessel walls as pressure is maintained and, to a lesser degree, to leakage I do not know if such an interpretation is correct, since extravascular factors, such as pulmonary edema, might influence pressure-volume relations

We did study (29), a number of years ago, the relationship between flow and pressure in normal individuals, and in patients after pneumonectomy In Figure 53, the flow through one lung of a normal individual is assumed to be half of the total flow, and this data is compared to the total flow which takes place through the single lung of individuals after

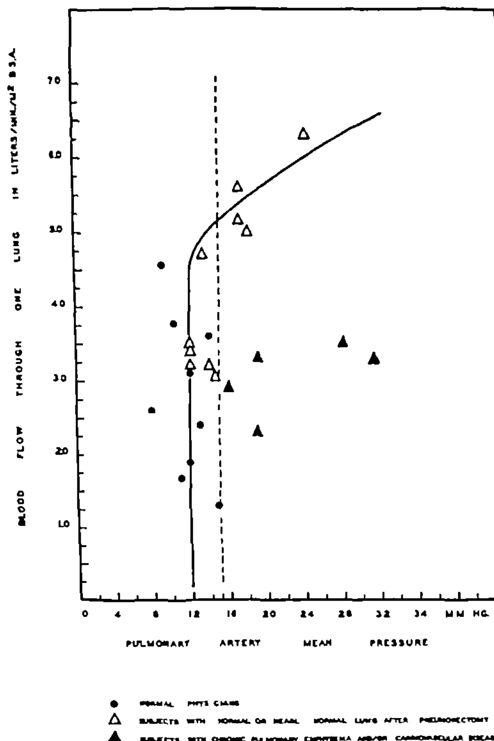



FIGURE 53 Relationship between blood flow through one lung and pulmonary artery pressure Reprinted by permission, from Cournand A Riley R L. Himmelstein, A. and Austrian, R Pulmonary circulation and alveolar ventilation perfusion relationships after pneumonectomy *J Thoracic Surg* 19 *80 (1950)*

pneumonectomy Even though the flow is twice that in the normal lung, it can be seen that there is no difference of pressure under resting condition But during exercise there is a significant increase in pressure in patients with one single lung, since the total flow attains value which we do not obtain in each lung of the normal subjects There is, however, a criticism to be made to these observations, that is that the normal subjects were exercised in the standing position but the patients after pneumonectomy were exercised in the supine position It is probable that under dynamic conditions, the volume of blood in the lung vessels might be significantly different in these two positions

*Burton* Do you correct the pressures measured to the catheter tip or to heart level?

*Cournand* To heart level

*Burton* So they are corrected for the difference in the hydrostatic pressure?

*Cournand* That is right As a matter of fact, there are many questions related to the problem of hydrostatic level should one take the center of the heart or the highest point in the right ventricle? We always try to take the same point but there are probably some variations in different individuals

*Burton* From the point of view of the size of an individual vessel, all it 'knows' is what the pressure is there, and from that point of view perhaps one should use the pressure corrected to the level of the end of the catheter It is the pressure there, which you are recording, which determines whether that vessel is open or how widely open, rather than a corrected pressure

*Cournand* Yes

*Burton* So that one is always in doubt as to whether one should make this correction or not according to what aspect one is interested in

*Cournand* That is right We took that into consideration In the supine position we take the center of the heart, not the tip of the catheter as we did once many years ago for the right atrium In the upright position we took the level of the catheter as the reference point I would say that in the flat position it would make very little difference

*Barcroft* Am I right that there are large blood flows in exercise in the patient after pneumonectomy but there are not such large blood flows in severe exercise in normal subjects?

*Cournand* That is right Indeed this is a very artificial curve, since we assume that in normal subjects the flow through each lung is half the total flow and since pressure variations in the normal are related to one half the flow at rest and during exercise After pneumonectomy, the total flow through the remaining lung during a light exercise is

much larger than the flow through each lung in a normal subject during very severe exercise We took advantage so to speak of this unusual situation to prolong the curve toward flow levels not attainable in normal subjects in the course of cardiac catheterization

Perhaps this is the time to mention that there is a dual circulation in the lung with anastomoses between both circuits I personally have no experience concerning this subject but maybe some of you have Dr Liebow and his associates (30) at Yale Medical School have been studying the bronchial circulation anatomically and to some extent dynamically, in health and in disease They have been impressed by the potentiality for the bronchial circulation to take over part of the pulmonary circulation in some pathological conditions of the lungs

The normal flow through the bronchial circulation in a normal dog is approximately 30 ml per minute or about 1 per cent of the total systemic flow a figure which corresponds grossly to the estimated flow through the bronchial circulation in man After ligation of one pulmonary artery the astronomical figure of 2 liters of blood has been estimated to flow per minute through the greatly expanded bronchial circulation I am somewhat doubtful of such figures which have been obtained on the basis of an indirect method i e bronchospirometry From an experience of over 15 years with this method I venture to say that measurements of oxygen uptake of each lung measured separately which serves as an index of the separate flows are liable to considerable error even in the hands of experienced investigators if the catheter is not partitioning tightly both main bronchi This I shall try to elaborate on later

*Gregg* May I add that Dr Henry Williams in our laboratory has repeated some of these studies measuring retrograde flow directly and has found a good sized increase in backflow—possibly 200 ml /min The flow values did not approach 2 liters/min

*Cournand* It is increased but not so much?

*Gregg* Yes

*Wilkins* What was the experimental condition that caused the increase?

*Cournand* Ligating one pulmonary artery then measuring the oxygen uptake by the lung on the assumption that the bronchial circulation has taken over Of course arteriovenous differences are very small since the bronchial artery blood returns to the lung almost completely saturated However there is no doubt that in diseases of the bronchi with severe inflammatory process the bronchial circulation increases

*Bing* In patients with complete pulmonary atresia, the bronchial circulation provides the entire pulmonary flow

*Cournand:* In my laboratory we have studied a patient with patent *ductus arteriosus*, after ligation of one pulmonary artery of an absolutely normal lung, necessitated by severe tear in the course of the surgical treatment of this defect. After a few months, the amount of oxygen uptake through this lung as determined by bronchospirometry was indeed somewhat increased, but far from attaining the values observed in dogs.

The problem of anastomoses between bronchial and pulmonary circulations bears out some questions raised previously. Particularly concerning pulmonary artery wedge pressure measurements, there is no doubt that if large anastomoses exist, the question of what is actually measured becomes infinitely more difficult to assess.

These anastomoses are of two orders: (*a*) direct anastomoses isolated by Von Hayek (31), under the name of "sparen" arteries, with a spiral musculature not unlike that described in the wall of the patent *ductus arteriosus* of the newborn, they constitute potential shunts between vessels of 100 to 200 microns, and (*b*) capillary anastomoses at the level of the respiratory bronchioles which drain blood to the pulmonary veins.

May I say that little is known about the metabolism of the matrix of the lung, but it is likely that metabolites and oxygen are provided by the bronchial rather than by the pulmonary circulation.

## CHANGES IN PULMONARY CIRCULATION AT BIRTH

So far, I have discussed very little of my own work, but as I believe this discussion is the first concerning the pulmonary circulation, a brief mention of general topics might help orient those among you who are not familiar with the subject.

The question of the changes in the circulation which take place at birth may be of great interest in an interpretation of the normal and abnormal physiology of the pulmonary circulation in the adult. You are, of course, all familiar with the superb work with lambs by Joseph Barcroft who actually demonstrated that most of the fetal and placental returning venous blood bypassed the lungs by the way of the *foramen ovale* and *ductus arteriosus* (*botali*) and followed the changes immediately after birth, particularly the rapid closure of the patent *ductus arteriosus*. More recently, Dawes *et al.* (32) have followed these changes, using in particular the technic of blood sampling and $O_2$ determination in various parts of the circulation to map flows and shunts as is currently done in the diagnosis of congenital heart disease. According to their work, 10 per cent of the total circulation goes to the lungs and, interestingly enough, the $O_2$ content of the pulmonary venous

blood is less than that of the artery In other words the pulmonary artery supplies the oxygen to the lung

They calculated that approximately 35 per cent of the venous return goes through the *foramen ovale* and 15 per cent through the patent *ductus arteriosus* The summation of percentage flows comes out fairly well considering that mixing equations are used At birth the *foramen ovale* apparently closes as soon as the pulmonary circulation is established apparently due to the increased pressure in the left atrium attendant to the pulmonary venous return They do not agree that the closure of the patent *ductus arteriosus* takes place very early There may be some species differences the closure being earlier in dogs than in lambs Whether the mechanism of closure is initiated by the increase in $O_2$ content of the aortic blood is still debated Of course the closure of the *foramen ovale* is strictly on a hemodynamic basis and is facilitated by the drop in right atrial pressure following ligation of the umbilical vein Conditions met in adults are easily obtained namely a higher pressure in the left than in the right atrium

With regard to the closure of the patent *ductus arteriosus* three points deserve mention (*a*) the spiral like distribution of the muscular coating (*b*) the nerve supply to this musculature the role of which is in doubt, and (*c*) the increase in O content in the aortic blood at the time of closure

Within a few minutes the patent *ductus arteriosus* closes some data given to indicate that the closure takes place after several days in the human newborn are based on a comparison of the $O_2$ content in the blood sampled simultaneously in the right brachial and in a femoral artery This takes advantage of the fact that the patent *ductus arteriosus* opens at the level of the left subclavian artery and that therefore persistence of flow through the *ductus* tends to reduce the $O_2$ content of the sample in the femoral artery as compared to that of the right brachial artery This has been used by Dr Wood and by our group to demonstrate reversal of flow in the adult patent *ductus* However in the study of the human newborn many errors might be introduced by this technic Lind and Wegelius (33) who have studied the closure of the patent *ductus arteriosus* in the human newborn by injection of opaque substances which takes a great deal of skill have shown that closure occurs a few minutes following the establishment of ventilation

## NERVE CONTROL OF THE PULMONARY CIRCULATION

A problem of considerable interest is that of the nervous control of the pulmonary circulation In talking with Dr Burton I found comfort in his agreeing that in this particular circulation changes in resistance do not necessarily mean changes in radius of the small vessels under the

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something than he saw somewhere else and in my opinion this is totally irrelevant What we really need are statements of the anatomy of the vessel as you said the position along the lengths of it the amount of smooth muscle the innervation what kinds the amount of force that it can exert and the stimuli which trigger it off

Many times you can apply stimuli which give desired results somewhere else but you do not obtain any response at a given place therefore the failure to obtain a response to one set of drugs does not mean the system cannot respond It may mean you are using the wrong stimulus

*Cournand* W Hamilton (31) has studied the effects of epinephrine in the intact dog and does not believe that it has an effect on the pulmonary vessels themselves Perhaps Dr Barcroft would like to say something on the effect of epinephrine on the pulmonary circulation

*Barcroft* No I have no experience

*Cournand* I am sorry It is a very interesting field I believe and not much is known

In some diseases associated with pulmonary hypertension sympathetic blocking agents have been reported to cause marked drops in the pulmonary artery pressures But let us point out (*a*) that these agents cause a marked vasodilation in the systemic circulation and (*b*) that small changes in blood volume within altered pulmonary vessels might cause large changes in pressures Therefore a drop in pulmonary artery pressure does not necessarily mean that it is the result of vasomotor activity

*Barcroft* Might I ask you whether or not Goldenberg (35) found that in infusions of arterenol in hypertensive patients there was quite a considerable rise in pulmonary circulation pressure? Do you remember that point?

*Cournand* He has shown that There was no measurement of output if I remember

*Wilkins* However the same objection that Dr Cournand just mentioned with drugs that lower systemic pressure applies here Arterenol raises systemic pressure so much that any effect that you obtain in pulmonary circulation can easily be interpreted as a back pressure effect

Exactly the same thing occurs (as we have reported (36) and others have confirmed) with angiotonin, which is a different kind of pressor agent. You cannot draw conclusions regarding the action on the pulmonary circulation of either a pressor or depressor drug given into the general circulation from what it then does to the pulmonary pressures

*Cournand* I am glad of Dr Wilkin s comment since it does orient the problem well Any constrictor or dilator effect on the systemic circu

control of vasomotoricity Clinicians are apt to equate the one to the others

It is impossible to survey the ground covered in recent years by physiologists and clinical investigators concerning the reaction of the pulmonary circulation to various drugs Let us say that there is much confusion because of differences in interpretation

*M Knisely* You asked what I thought about the smooth muscle on the artery a while ago May I ask you now how you expect drugs to work in a place where there isn't any muscle?

*Cournand* I have not said that there is no smooth musculature in the pulmonary circulation, but rather that "arterioles" have no smooth musculature Larger arteries have such a musculature My distinction between systemic and pulmonary circulation was meant to emphasize that you cannot speak in the latter circulation of arteriolar stopcocks The site of smooth musculature is on vessels of a larger diameter than arterioles

*Wilkins* Is that only in normal lung or also in diseased lung as in people with mitral stenosis?

*Cournand* Pathologists often hesitate actually to define the vessels that they are seeing under the microscope As mentioned earlier, arterioles usually less than 100 microns have a very thin wall and their internal diameter may be even larger than that of small muscular arteries This is in contrast to what is seen in the fetus where the *media* of the small arteries is thick and the lumen very small In mitral stenosis, the small caliber vessels acquire a thick *media*, but pathologists will hesitate to define them further

To mention the effects of drugs, in human subjects the results are very conflicting The drugs mostly tested have been epinephrine, arterenol, and a few synthetic blocking agents but aside from measurements of flow and pressures in the pulmonary artery, including wedge pressures, there is little information as to what happens to pulmonary blood volume or in the left heart and systemic circulation Yet to decide whether the effect of a drug is related to vasomotor control, all this hemodynamic information is required, particularly that involving blood volume displacement from one circulation to the other, as a result of its effect on the systemic vessels

*M Knisely* There are species, and I think the mouse is one, in which two injections of an antigenic material cause the pulmonary artery to contract until nothing goes through at all I am always charmed by statements about how much smooth muscle there is on a blood vessel because they are frequently made with implications that the vessel can or cannot contract because someone has or has not seen more or less of

and of tracheobroncho-alveolar gas has become so complex as almost to defy imagination Briefly presented this concept states that alveolar O tension has an effect upon the capillary and postcapillary segment of the pulmonary vascular bed and mixed venous O tension has an opposite effect upon the precapillary segment (dilation) Furthermore CO in the gas and blood phases has opposite effects to that of $O_2$ in these phases respectively and finally $O_2$ tension in the tracheobronchial tree would indirectly affect flow by changes in the compliance of the lungs In other words the maintenance of vascular resistance is the result of a set of coupled and opposite influences For those with imagination such a concept is tempting but it will also require imagination to see how it could work

In normal man we (10) have observed the same phenomenon, namely that anoxia causes a rise in pulmonary artery pressure which is not accounted for by a sufficiently large increase in pulmonary blood flow

Rahn and Bahnson (42) among other studies on this subject in dogs have tried to find out what happens when one lung only is ventilated with a low-oxygen mixture On the basis of indirect data which requires a very involved although extremely elegant interpretation of a gas exchange diagram, they concluded that in the dog anoxia caused a shift of blood (increased resistance) toward the normal lung This supported the observations of Dirken and Heemstra (43) on the rabbit in which the arterial blood oxygen saturation returns to normal after 6 to 8 hours when one lung is breathing nitrogen

I would like to mention here that I agree with Rahn that in normal man variations in carbon dioxide tension in the lungs has no effect upon the pulmonary arterial pressure

As shown in Figure 54 if there is an effect in pulmonary disease this may be accounted for by a significant increase in pulmonary blood flow taking place in a reduced vascular bed In this figure the dark block represents pressure and flow before breathing a mixture of 5 per cent $CO_2$ in air and the white blocks the same measurements while breathing this mixture. In normal subjects there is no significant change in flow or pressure In the patients with pulmonary disease whether the pulmonary arterial pressure is high or normal to start with if there is no increase in flow there is no further change in pressure in the pulmonary artery In the same patients the least degree of exercise caused a marked increase in pressure

*Merriman* What is the final group?

*Cournand* These are patients with more extensive pulmonary disease in whom the least increase in flow because of physical activity caused

lation may cause displacement of blood from one circulation to the other. In the normal pulmonary circulation, drugs will be said to have a striking effect if the pressures vary by 5 to 10 mm. Hg at most, but normal variations in pressures may amount to 3 mm. Hg and the error in reading curves is of the same order, so that the margin of confidence is small indeed.

*M. Knisely:* Have there been studies by competent neurological methods aimed at finding tips of fibers and the tips of nerve endings up and down this vascular tree?

*Cournand:* There has been some work regarding the receptor, but little, to my knowledge, regarding the effector.

*Merriman:* Hasn't Dr. Geoffrey S. Dawes* made studies along that line?

*Barcroft:* I cannot recollect any neurological work.

*Merriman.* Those are receptor, not effector, methods.

*Burton:* His interest has been confined to the region near the heart and pulmonary artery.

## EFFECTS OF ANOXIA UPON THE PULMONARY CIRCULATION

*Cournand:* In 1942, Beyne (37), a French physiologist and a pupil of Binet, demonstrated in the isolated lung of dogs that, at a constant pulmonary blood flow, the pulmonary artery pressure rose when the animal was breathing a low oxygen mixture. This appeared to be the first experiment on the effect of hypoxia, until I was shown, while in Germany, a photostatic copy of a report of Gauer and Wagner to the Luftwaffe, demonstrating a systolic pressure rise in the right ventricle of dogs during hypoxia. In 1946, von Euler and Liljestrand (38) published an extensive and well documented study on the effects of the gaseous composition of the alveolar gas upon the pulmonary circulation. These studies did not include measurements of blood flow, and the anoxic stimulus was claimed to be local without intervention of nervous reflexes. Indeed, as a result of their own and of their collaborators' investigations, Liljestrand, in 1948 (39), and von Euler, in 1951 (40), pointed out a new physiologic mechanism whereby the local gaseous composition within separate units of the lungs could, without intervention of the autonomic nervous system, regulate local alveolar perfusion. As a result of further studies by Nissel (41), the regulation of alveolar perfusion by variations in gaseous composition of the circulatory blood

*Dr. Dawes is at the Nuffield Institute for Medical Research, University of Oxford, Oxford, England.

marked increase in pulmonary artery pressures. Similarly in those cases where pulmonary flow increased during CO breathing and only in those cases did the pressure rise.

Only two cases in the whole series showed a pressure rise without increase in blood flow, the pressure variations being at the limit of significance.

*Montgomery:* These changes are all the result solely of inhalation of 5 per cent carbon dioxide?

*Cournand:* That is right, 5 per cent.

*Montgomery:* And the exercise part is solely to classify the patients?

*Cournand:* I say, as a possible explanation for the increase in pressure, that the same increase in flow resulting from exercise has shown, in this same individual, a pressure rise.

*Kety:* Dr. Cournand, what do you think is the significance of the increase in flow in the two patients with only one lung?

*Cournand:* I have no immediate explanation but it seems significant now that you call attention to it. This may be due to a marked increase in ventilation.

In Figure 55, taken from a paper by Rahn and Otis (11), the time required for the $O_2$ uptake and the respiratory quotient to return to the control levels during the breathing of a 13, 11, and 10 per cent oxygen

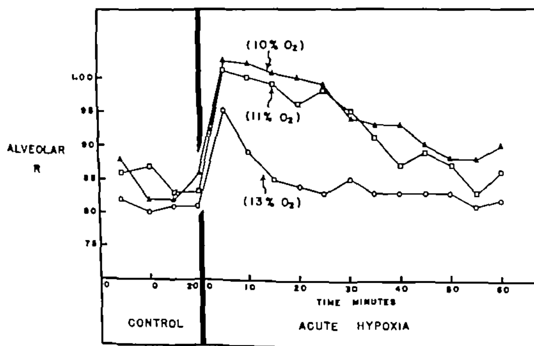



FIGURE 55. Time required for the respiratory exchange ratio to return to normal during acute hypoxia.

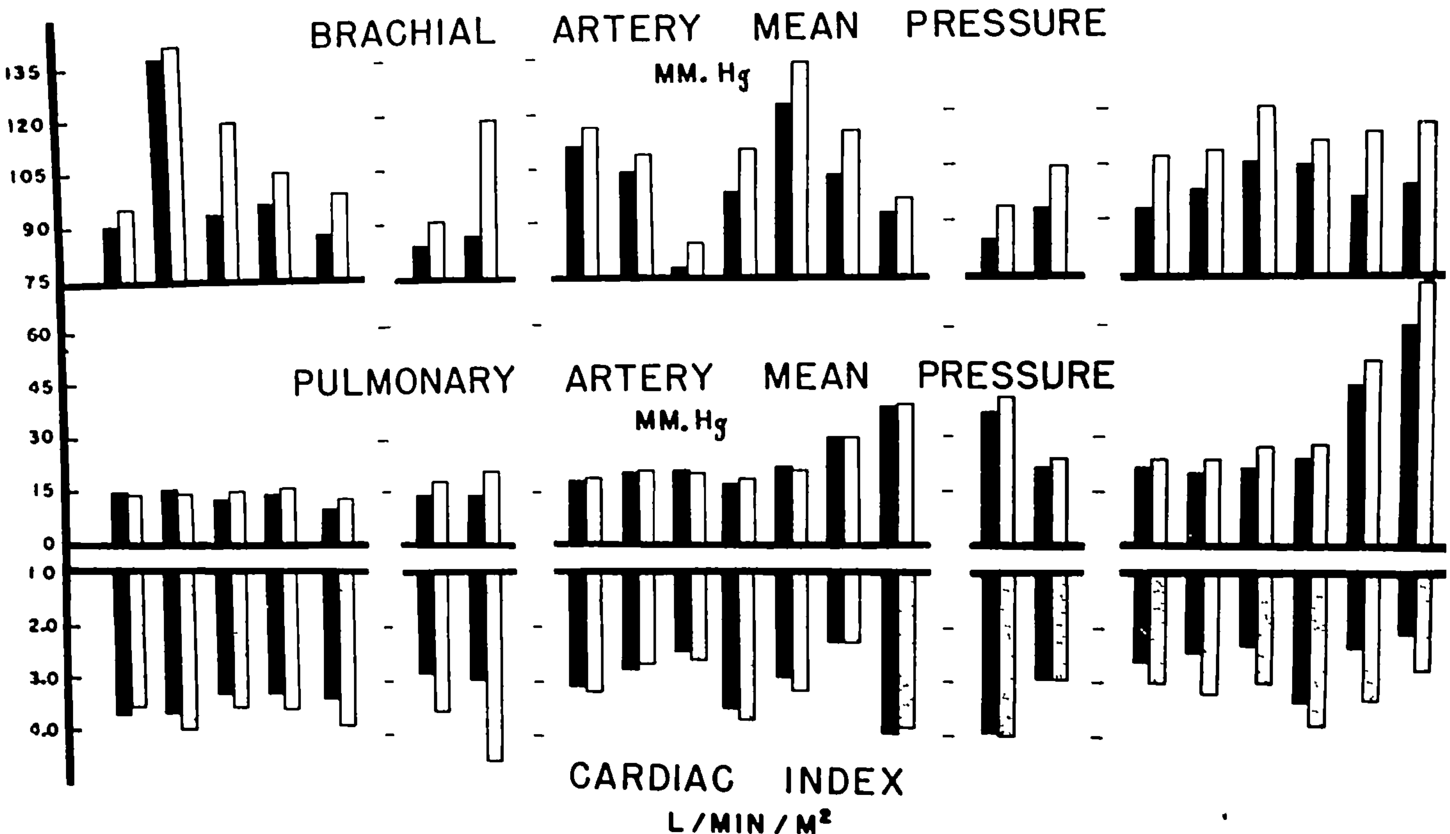



FIGURE 51 The effect of breathing $CO_2$ on the pulmonary and systemic flow and pressures Fishman, A P, Fritts, H W, Jr, Himmelstein, A, and Cournand, A (Unpublished data)

## TABLE XIII

**Gas Exchange-Hemodynamic Variation Following Acute Hypoxia***

| | 21 % $O_2$ | 11 % $O_2$, 5 MIN | 11 % $O_2$, 17 MIN | 11 % $O_2$, 20 MIN |
|---|---|---|---|---|
| $Sa_{O_2}$ % | 95 | 71 | 59 | 59 |
| $V_{O_2}$ ML/MIN | 203 | 165 | 188 | 191 |
| $C_a - C_v$ ML/100 ML | 4 2 | 3 5 | 3 1 | 3 3 |
| $\bar{Q}$ ML/MIN | 4800 | 4710 | 6060 | 5790 |
| $R_p$ | 95 | 1 23 | 1 00 | 99 |

*Fishman, A. P, Fritts, H W, Jr., Himmelstein, A, and Cournand, A (Unpublished data)

in air, is well illustrated A period of more than 30 minutes is required while breathing the 10 per cent mixture and therefore application of the Fick formula to data obtained in the changing state before this period of time has elapsed is unwarranted

*In Table XIII, the same point is illustrated in data obtained in my* laboratory in collaboration with Fishman, Fritts, and Himmelstein It shows that figures for $O_2$ uptake, $V_{O_2}$, arteriovenous difference, $Ca_{O_2}$ $Cv_{O_2}$, and respiratory quotient, $R_E$, still vary after 5 minutes, and that blood flow, Q, calculated from these figures would be totally misleading

In Table XIV, however, all measurements of the circulation were made at a time when a new steady state had taken place after anoxic breathing had been initiated The flow increase is the greater the greater the reduction in arterial blood $O_2$ saturation, $Sa_{O_2}$

As for the pressure rise in the pulmonary artery, there is also, as seen in Table XV, a gross relationship between the increase in pressure, the increase in flow, and the drop in arterial blood $O_2$ saturation For instance, in one individual where arterial blood $O_2$ saturation declined to 60 per cent, the pulmonary artery pressure rose by 12 mm Hg while the flow increased by 20 per cent But the relationship is not always so straight Hurlimann and Wiggers (44), who have studied this problem *of anoxia upon the pulmonary circulation in dogs, have concluded* that besides the flow changes, there is some additional factor to explain the pressure rise in the pulmonary artery

To emphasize the probable role of the arterial anoxemia, data are presented in Figure 56 which seem to indicate that in patients with pulmonary emphysema, the pressure in the pulmonary artery is related to the degree of arterial blood $O_2$ unsaturation

The effects of exercise and of acute anoxia upon pulmonary blood flow and pressure are compared in Figure 57 The mean blood flow changes during exercise, although greater than during hypoxia in the same five individuals, resulted in a much lower pulmonary artery blood pressure rise, obviously, besides the increase in blood flow, some other factor must play a part in the latter state In the right part of the same figure, it is interesting to point out that in individuals with one single normal lung and therefore with a much reduced vascular bed, the increase in blood flow alone, in both exercise and anoxia, might explain the pulmonary artery pressure rise

Since an increase in precapillary resistance may be invoked to explain the pressure rise in the pulmonary artery, and since the variations in the mixed venous blood $O_2$ tension may have some effect upon the walls of the precapillary pulmonary bed, Dr Fishman, Dr Fritts, and Dr Himmelstein (45), to whom I owe much for their help in the studies pre-

## TABLE XV

### Pulmonary Artery Pressure and Flow During Acute Hypoxia in Normal Subjects

| Subject | Inspired Oxygen per cent | $Sa_{O_2}$ | Pulmonary Artery Mean Pressure | | Cardiac Index | |
|---|---|---|---|---|---|---|
| | | | Control mm Hg | Hypoxia mm Hg | Control l min/m² | Hypoxia l min/m² |
| H P | 12 | 76 | 16 | 20 | 2.86 | 3.22 |
| H R | 12 | 60 | 15 | 27 | 2.90 | 3.51 |
| A F | 11 | 71 | 10 | 14 | 3.31 | 3.55 |
| H P | 12 | 65 | 17 | 23 | 3.87 | 4.49 |
| B J | 14 | 87 | 11 | 17 | 3.13 | 3.40 |
| E J | 14 | 85 | 11 | 14 | 4.30 | 4.68 |
| G H | 12 | 84 | 10 | 15 | 3.50 | 4.08 |
| H M | 12 | 78 | 18 | 31 | 2.63 | 3.43 |
| Mean | | | 14 | 20 | 3.35 | 3.80 |
| | | | +6 mm Hg | | +12% | |

Fishman, A. P, Fritts, H. W., Jr, Himmelstein, A., and Cournand, A. (Unpublished data)

ditions of unilateral hypoxia, have endeavored to estimate the $O_2$ tension in the pulmonary venous blood leaving the hypoxic lung by an equilibration technic We completely broke with this tradition

The mixture given to one lung was 25 per cent oxygen in nitrogen With such a mixture it can be assumed and easily demonstrated that the pulmonary venous blood leaving the lung is fully saturated and that the amount of $O_2$ in solution in the plasma is not greater nor less than that of arterial blood of the same subject after equilibration with room air at sea level.

Under these conditions the oxygen content of the pulmonary venous blood of the lung breathing a mixture of 25 per cent oxygen in nitrogen is considered to be identical to the oxygen capacity of the arterial blood Should the breathing mixture be significantly higher this no longer would be true This being a crucial assumption, I would like to hear any question that may be raised

## TABLE XIV

### The Effect of Twenty Minutes of Hypoxia Upon the Pulmonary Blood Flow

| Group | Number of Cases | State | $Sa_{O_2}$ % | R | $V_{O_2}$ ml/min/m² | Q l/min/m² |
|---|---|---|---|---|---|---|
| I | 5 | Control (1) | 96.4 | 85 | 138 | 3.40 |
| | | Hypoxic (2) | 82.4 | 94 | 143 | 3.81 |
| II | 9 | Control (1) | 95.0 | 87 | 125 | 2.92 |
| | | Hypoxic (2) | 69.9 | 99 | 125 | 3.54 |

Fishman, A. P., Fritts, H. W., Jr., Himmelstein, A., and Cournand, A. (Unpublished data)

sented here, analyzed the data in all individuals in whom exercise and acute anoxia were induced successively. They retained four cases in whom the mixed venous blood $O_2$ tensions were identical in both states. The results pictured in Figure 58 show clearly that although during exercise the pulmonary blood flow was much larger than during acute anoxia, the pressure rise was somewhat less.

Although this is indirect evidence, it would seem fair to conclude that variation of $O_2$ tension in the mixed venous blood is not the factor which solely determines pulmonary artery pressure rise by increasing the precapillary vascular resistance.

We come now to what constitutes the most interesting approach to the problem of the effects of acute hypoxia upon the pulmonary circulation in man. Although we had been planning these experiments for many years, it is only in the past 2 years that, with the joint efforts of Fishman, Himmelstein, and Fritts (45), cardiac catheterization and bronchospirometry were actually performed simultaneously in the same individuals and became part of a method for the determination of blood flow through each lung separately. Of course, the considerable skill and experience of Himmelstein with both technics assured its success with a minimum of risk. Very efficient teamwork was also required. The method has been described elsewhere in detail (46) and only a few important points will be made here.

So far, all investigators who used the bronchospirometric method in order to determine blood flow through each lung separately, under con-

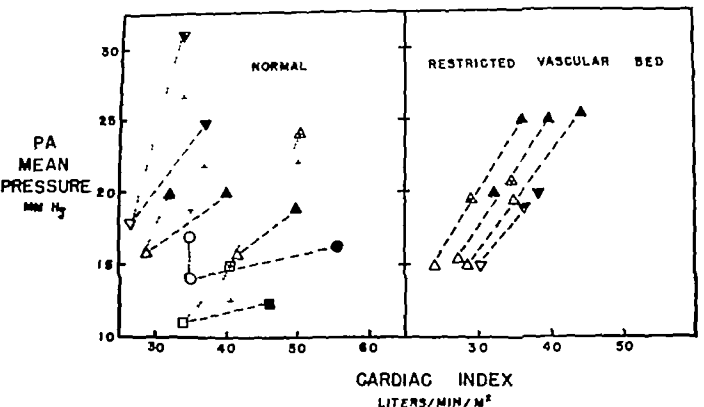



FIGURE 57 P A. pressures and flows during acute hypoxia and exercise in steady state Fishman, A. P., Fritts H W Jr Himmelstein, A. and Cournand, A. (Unpublished data)

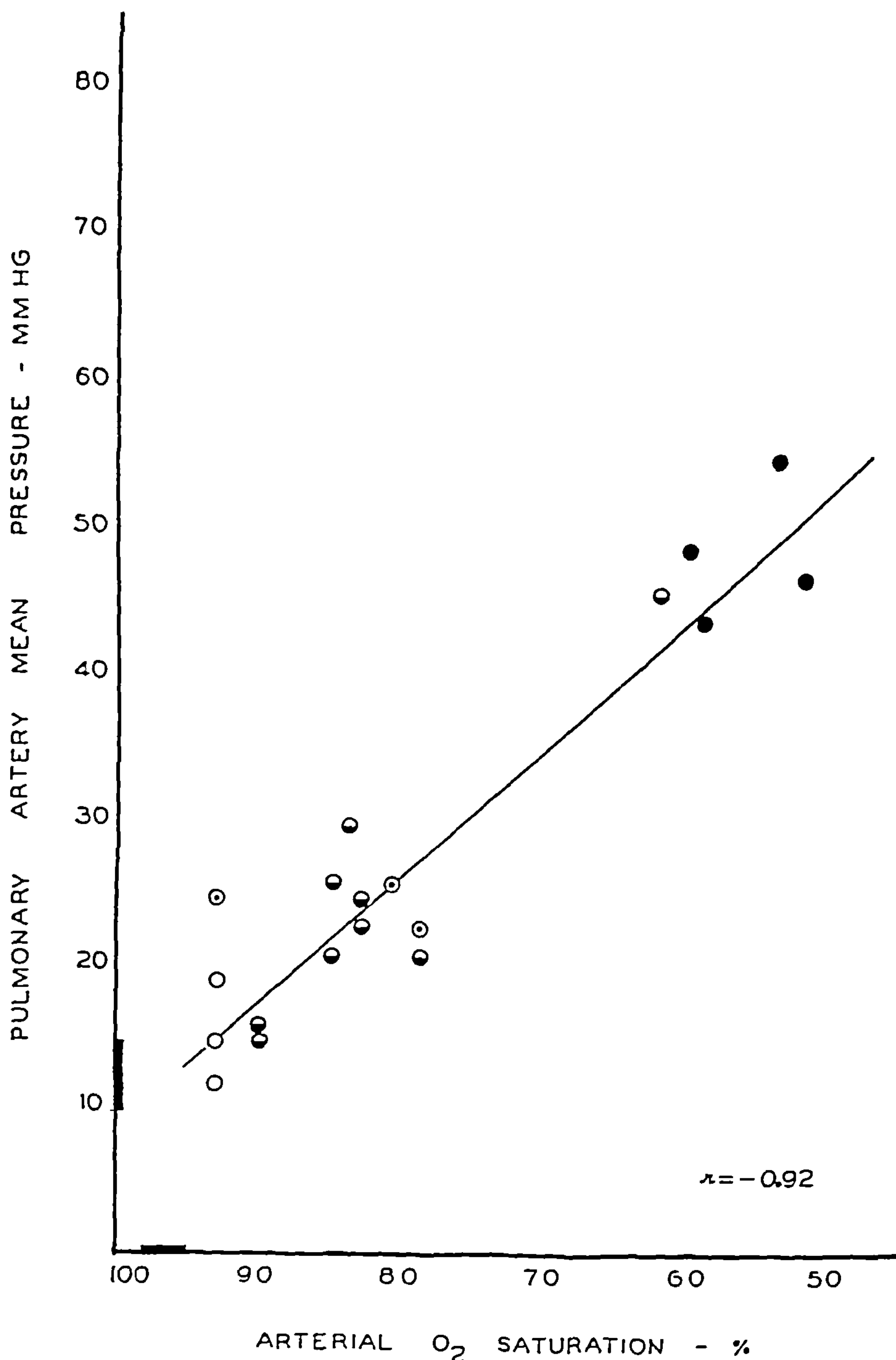



FIGURE 56 Relation between arterial oxygen saturation and mean pulmonary arterial pressures in chronic pulmonary emphysema Reprinted, by permission, from Cournand, A. Fourth Walter Wile Hamburger memorial lecture, Institute of Medicine of Chicago, some aspects of pulmonary circulation in normal man and in chronic cardiopulmonary diseases *Circulation 2, 641, (1950)*

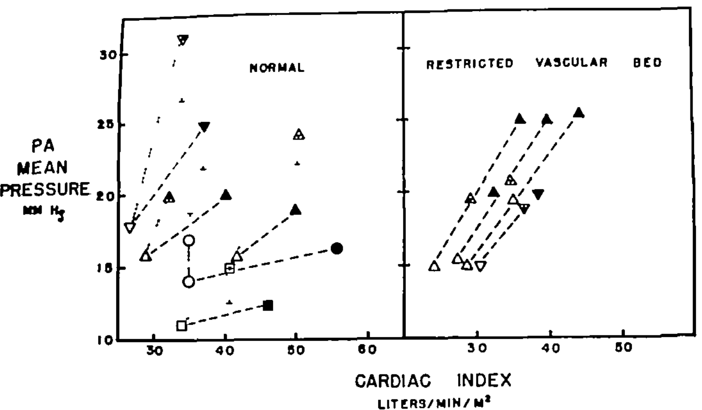



FIGURE 57 P A. pressures and flows during acute hypoxia and exercise in steady state. Fishman, A. P Fritts H W Jr Himmelstein, A and Cournand, A. (Unpublished data)

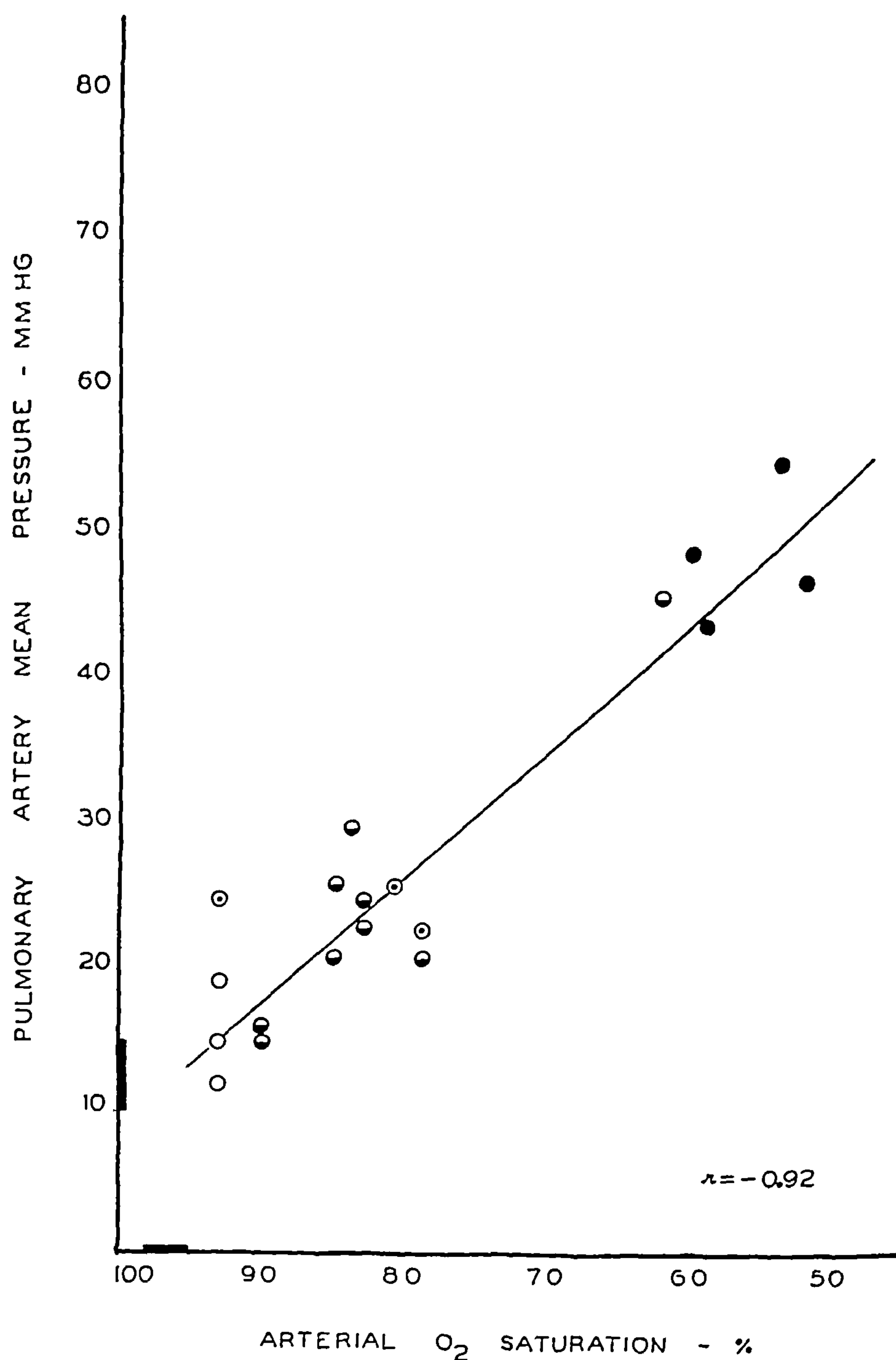



FIGURE 56 Relation between arterial oxygen saturation and mean pulmonary arterial pressures in chronic pulmonary emphysema Reprinted, by permission, from Cournand, A Fourth Walter Wile Hamburger memorial lecture, Institute of Medicine of Chicago, some aspects of pulmonary circulation in normal man and in chronic cardiopulmonary diseases *Circulation 2, 641, (1950)*

$$Q_T = \frac{(Vo_{2\,H} + Vo_{2\,L})}{(Ca_{O_2} - C\bar{v}_{O_2})}$$

$$\dot{Q}_H = \frac{Vo_{2\,H}}{(CAPa_{O_2} - C\bar{v}_{O_2})} \qquad Q_L = Q_T - Q_H$$

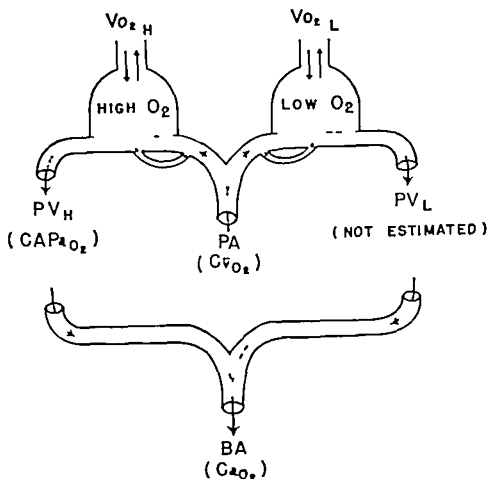
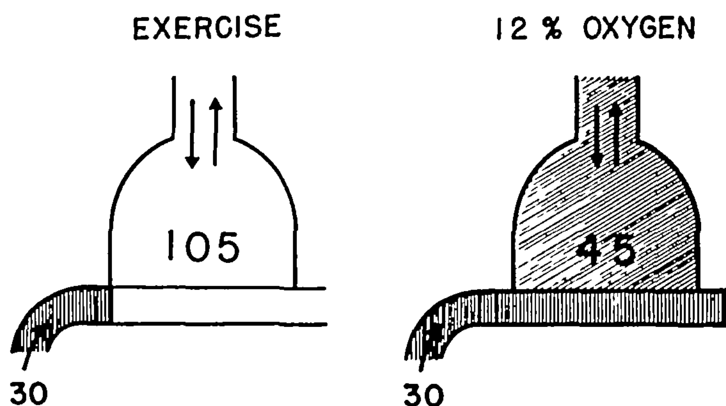



FIGURE 59 Schematic representation of a method for measurement of separate pulmonary blood flow through each lung Reprinted, by permission, from Fishman, A. P., Himmelstein A Fritts H W Jr and Cournand, A Blood flow through each lung in man during unilateral hypoxia *J Clin Investigation* 34, 637 *(1955)*

breathing air the day before and assume that pulmonary vein blood was the same the day of the experiment?

*Cournand* Because we endeavor to be as accurate as possible The




| | EXERCISE | 12 % OXYGEN |
|---|---|---|
| MEAN PA PRESSURE MM Hg | 19 | 21 |
| MEAN CARDAC INDEX ML/MIN/M² | 4.67 | 3.54 |

FIGURE 58 Mean PA pressure and flow in four normal subjects at same mixed venous $pO_2$ during exercise and hypoxia Fishman, A P, Fritts, H W, Jr, Himmelstein, A, and Cournand, A (Unpublished data)

*Wilkins* Pulmonary venous blood means wedged catheter blood Is that how you get it?

*Cournand* No, the pulmonary venous blood is assumed to have the same composition as the arterial blood after equilibration with room air While breathing 25 per cent $O_2$ in nitrogen, the error cannot be greater than 0 1 volume per cent

*Kety* That also assumes, then, that the ratio of ventilation to perfusion remains the same when one lung is hypoxic as it was when both lungs were breathing the same oxygen tension

*Cournand* Even if it changed, it would not make any difference in the calculation of separate pulmonary blood flow

The principle of the method and the calculations are presented in Figure 59 Total pulmonary blood flow is calculated with the usual data $O_2$ uptake of both lungs, and arteriovenous $O_2$ content difference The flow through the lung breathing 25 per cent $O_2$ in nitrogen, is calculated using (*a*) the $O_2$ uptake of this lung measured separately, and (*b*) arterial blood $O_2$ capacity—mixed venous blood $O_2$ content difference The flow through the other lung, whatever mixture it breathes, room air or low oxygen, is calculated by difference

*Wood* What was the objective of getting the arterial blood 100 per cent saturated? Why couldn't you have made the determination when

## TABLE XVI

### Successive Determinations of Total Blood Flow and Blood Flow Through One Lung Prior to and During Unilateral Hypoxia

| Subject | State | Time of Exposure min | $Q_T$ l/min | $Q_L$ l/min | $\frac{Q_L}{Q_T} \times 100$ |
|---|---|---|---|---|---|
| H J | Control | 10 | 5 75 | 2 67 | 46 |
| | Control | 15 | 6 58 | 2 91 | 44 |
| | Hypoxic | 15 | 6 56 | 3 05 | 46 |
| | Hypoxic | 20 | 6 88 | 3 40 | 49 |
| D C | Control | 15 | 8 18 | 4 24 | 52 |
| | Hypoxic | 15 | 7 58 | 3 90 | 51 |
| | Hypoxic | 25 | 9 60 | 4 74 | 49 |
| | Control | 15 | 7 76 | 3 33 | 43 |
| G H | Control | 10 | 6 78 | 2 49 | 37 |
| | Control | 15 | 6 91 | 3 48 | 50 |
| | Hypoxic | 15 | 6 10 | 3 03 | 50 |
| P T | Control | 10 | 9 74 | 5 24 | 54 |
| | Control | 15 | 10 18 | 6 34 | 62 |
| | Hypoxic | 15 | 9 88 | 5 72 | 58 |
| | Hypoxic | 20 | 9 34 | 5 62 | 60 |
| J S | Control | 10 | 8 00 | 2 89 | 36 |
| | Hypoxic | 15 | 8 34 | 2 91 | 35 |
| | Control | 10 | 7 67 | 3 32 | 43 |
| R R | Control | 10 | 7 75 | 4 12 | 52 |
| | Control | 15 | 6 90 | 3 27 | 48 |
| | Hypoxic | 15 | 7 35 | 3 55 | 48 |
| | Hypoxic | 25 | 7 72 | 4 14 | 54 |

Reprinted by permission from Fishman, A P Himmelstein, A Fritts H W Jr and Cournand A Blood flow through each lung in man during unilateral hypoxia *J Clin Investigation* 34 637 (1955)

difference in pulmonary venous $O_2$ content while breathing room air as compared with 25 per cent $O_2$ might introduce an error of 3 or 4 per cent

*Wood* I would think your assumption, that the pulmonary vein blood was the same the day before when you were breathing the 25 per cent oxygen, would not have been any worse if you just let the person breathe air I do not see quite why that should cut down the error in the assumption I agree with you that probably the assumption will not seriously interfere with your experiment

*Kety.* The hemoglobin association curve is a little steeper at that point than it would be at 100 per cent, and the error might be somewhat larger

*Wood* Yes, that is true Of course, it is fiction that the hemoglobin is completely saturated at that tension (47), but it is a good point, you would get in a flatter portion of the dissociation curve

*Cournand* May I say, Dr Wood, that the A-V differences in these patients to whom we give atropine to avoid secretions are not great Furthermore, we must be assured that the alveolar $O_2$ tension remains around 120 to 130 mm Hg, otherwise the measured blood flow through that lung could be in serious error

In Table XVI the results of six experiments are summarized It shows that between the control period and the acute anoxic period, total, $Q_T$, and unilateral, $Q_L$, pulmonary blood flow did not change significantly

Furthermore, there was no increase in pulmonary artery pressure In summary, we can retain the following facts Under conditions of acute unilateral hypoxia associated with a limited degree of arterial blood hypoxemia, there was, (*a*) no shift of blood from the hypoxic lung, and (*b*) no pressure rise in the pulmonary artery

Aviado (48) and his collaborators have recently concluded from experiments on dogs that the pressure rise in the pulmonary artery associated with acute hypoxia is due to the effects of the reduced $O_2$ tension of the arterial blood upon the carotid body chemoreceptors, with stimulation of reflexes affecting the pulmonary vascular bed

Work actually under progress tends to show that with a greater reduction in arterial blood $O_2$ tension, a pressure rise in the pulmonary artery will occur under conditions of the experiment described above, but that complete denervation of the lung in man will not prevent the pressure rise

These, and other studies, actually in progress, concerning particularly the effects of anoxia upon the central blood volume, lead us to believe that the pressure rise in the pulmonary artery is probably accounted for

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by hemodynamic changes not involving vasomotoricity (*a*) the increase in flow and, (*b*) the encroachment upon the pulmonary artery distensibility associated with an increase in pulmonary blood volume

We have repeated anoxia studies after extensive sympathectomy with removal of the stellate, the first four dorsal, and, in one case, of the median cervical ganglia, the effect of acute anoxia persists The pulmonary pressure goes up in exactly the same manner

*Wilkins*· We have made the same observation Dr William Hollander and Dr Walter E Judson in our laboratory have studied this problem extensively and they finally came to the same method and showed that as far as we were able to determine the sympathetic nervous system, or at least that part that can be removed by surgery, from the stellate through the fifth dorsal ganglion, is not necessary for the appearance of the rise in pulmonary arterial pressure that occurs with 10 per cent oxygen breathing

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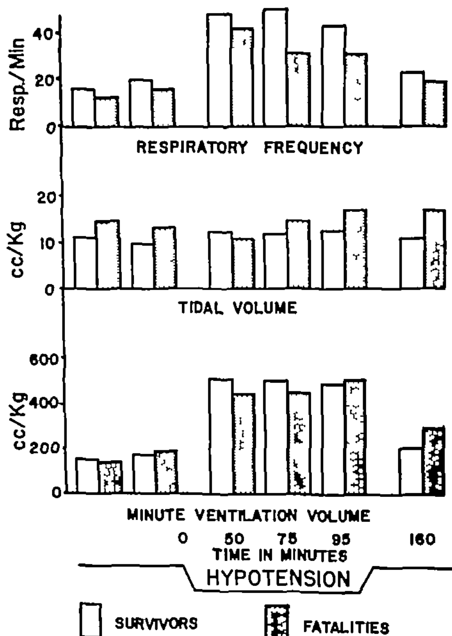



FIGURE 60 The respiratory frequency tidal volume, and minute ventilation volume for six observation periods during hemorrhagic hypotension Hypotension was maintained at 40 to 45 mm Hg for 55 minutes using a modified reservoir technic after which the reservoir was clamped off and the animal followed for a further 45 minutes After 65 minutes half the animals received priscoline After 100 minutes of hypotension all the reservoir blood was reinfused Dogs breathed room air throughout the experiment Nine survivors in open bars nine fatalities in stippled bars

groups on the basis of their dead space volumes during shock One group of three dogs had no significant change in the physiological dead

# THE PULMONARY CIRCULATION IN HEMORRHAGIC SHOCK

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DURING THE SUMMER of 1953, at the University of Western Ontario, I had the opportunity of studying some aspects of the pulmonary circulation in shock At that time the Department of Physiology* was investigating the problem of hemorrhagic hypotensive shock in the dog, using a modified Wiggers' technic (1) My results can be divided into two parts, the first dealing with the ventilation, and the second with the oxygen saturation of the arterial blood We have no adequate pressure measurements

## VENTILATION VOLUMES

The ventilation volumes were measured in eighteen experiments, with the animals breathing room air Figure 60 shows the average values The respiratory frequency, tidal volume, and minute ventilation volume are shown from above down The period of hemorrhagic hypotension (duration—100 minutes) is shown at the bottom of the Figure The nine survivors are shown in open bars and the nine fatalities in stippled bars You will notice that the minute volume of ventilation is markedly increased during shock and is approximately the same in both groups In the survivors, the respiratory rate is somewhat faster and the tidal volume somewhat less than in the fatalities

Hertzman (2), Henderson (3), and Wiggers (4) showed that the minute volume of ventilation increased markedly during shock, and the magnitude of this increase bore a close correlation to the severity of shock Our findings are in complete agreement In eleven of these dogs, additional measurements were made, which allowed the calculation of the volume of the physiological dead space

It was noted that these eleven dogs could be divided into three

*This work was aided, in part, by grants from the Defence Research Board of Canada and the Ontario Heart Foundation

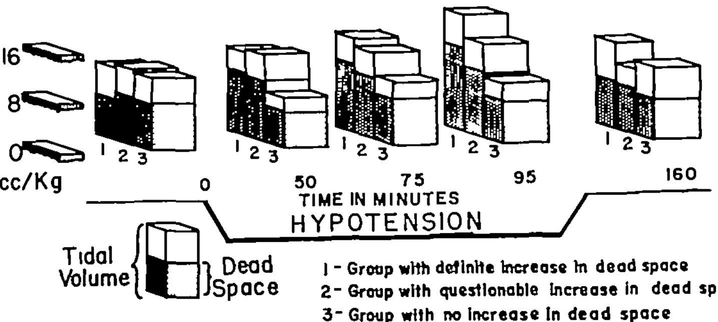



FIGURE 61 Tidal volume and physiological dead space changes during hemorrhagic hypotension Experimental design as in Figure 60 Physiological dead space calculated from the Bohr equation using the value for arterial carbon dioxide tension calculated from the Henderson Hasselbalch equation. Group 1—5 dogs group 2—3 dogs group 3—3 dogs

space during the experiment. Another group of five dogs had a definite increase in physiological dead space during the hypotensive period of shock, which returned to control values at one hour post reinfusion. The remaining three dogs had a slight increase in dead space during shock.

Figure 61 shows this difference graphically. There was no relation between survival and the increase in dead space volume. In this slide the mean tidal volume in ml./kg. is shown during the course of the experiment. The stippled area of the column represents the physiological dead space. The difference between the tidal volume and the dead space is the alveolar ventilation per breath. In group three, the dead space remains unchanged throughout the experiment, and the tidal volume actually decreases. In group one, the physiological dead space increases markedly during shock and at 95 minutes of hypotension, the mean dead space volume has doubled the control value, whereas the tidal volume has increased by 63 per cent. At one hour post-reinfusion, the values for physiological dead space and tidal volume have returned toward normal levels. The other group shows values which are in between.

*M. Knisely:* How did you initiate the shock?

*Merriman:* This was done by bleeding from the femoral artery into a reservoir until a hypotensive level of either 40 or 45 mm. Hg was obtained.

*Cournand:* Perhaps all the members of the group are not familiar with the dispute among physiologists concerning the definition of pulmonary dead space?

*Merriman:* Would you like to elaborate on this?

*Cournand:* Very briefly, the dead space ventilation is the equivalent of a volume of inspired gas which is not modified in its composition by contact with the circulating blood. It is not a spatial measurement but rather a dynamic measurement. Is this definition correct according to you?

*Merriman:* That is correct. In other words, the physiological dead space is that portion of the tidal volume that does not undergo gas exchange. Thus some animals showed an increase in dead space during shock, while other animals did not. In those in which the dead space increased, the tidal volume also increased.

It occurred to us that if more frequent observations of tidal volume could be made, more information might be gained about the dead space changes, since from our experiments, the alveolar ventilation per breath usually remained about the same, and a sudden increase in tidal volume might mean an increase in dead space.

An additional five experiments were made, this time with the dog in-

## TABLE XVII

*Measurements During the Early Hypotensive Period on a Dog Inspiring Pure Oxygen*

DOG X 29 13 6 kg

| Time in Minutes | Control | 3-11 | 11 20 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 13 51 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tidal Volume | 264 | 137 | 118 | 135 | 131 | 137 | 112 | 155 | 171 | 190 | 195 | 201 |
| Respiratory Frequency | 4 8 | 21 6 | 47 6 | 50 | 48 | 49 | 45 | 41 | 38 | 33 | 30 | 39 3 |
| Minute Volume Inspired | 1241 | 2961 | 5605 | 6726 | 6270 | 6726 | 6381 | 6810 | 6612 | 6270 | 5871 | 7888 |

spiring pure oxygen Minute to minute values for respiratory frequency and total volume inspired, were taken for periods of 8 minutes, at frequent intervals during the experiment Dead space volumes, however, were not measured

In four out of these five experiments, we did observe that at some time during the first 30 min of hypotension, the tidal volume suddenly increased

In Table XVII, the values for tidal volume, respiratory frequency, and minute volume of inspired oxygen are shown for one of these dogs I would like you to notice particularly the change in tidal volume During the control period, the tidal volume was large associated with the very slow respiration rate During the early hypotensive period, the tidal volume decreased while the respiratory frequency increased From 24 to 27 minutes, the average tidal volume was 137 ml and the respiratory frequency, 47 per minute Following this, the tidal volume increased over a 3-minute period from 137 to 190 ml From 43 to 51 minutes of hypotension, the individual values for tidal volume did not differ significantly from each other and the mean value of 201 ml was very similar to the value at 31 minutes In this experiment, if our average value for dead space in ml /kg is used, and if it is assumed that the alveolar ventilation per minute remained the same from 24 to 31 minutes, then the volume of the dead space would have increased by 37 per cent On the other hand, if the value for dead space had remained unchanged, then the alveolar ventilation per minute at 30 minutes of hypotension would have increased by 63 per cent in an interval of approximately 3 minutes

I cannot say what happened to the physiological dead space in this case because I did not measure it However, the only conclusion one can safely draw from these experiments is that these figures are very interesting In retrospect, I wish additional measurements could have been made

Why, then, did some animals show an increase in physiological dead space during shock, which returned to control values at one hour post reinfusion? This means, by definition, that an additional portion of the tidal volume did not undergo gas exchange This could only occur if some alveoli were ventilated, but not perfused In other words, the flow of blood must have ceased through a portion of the pulmonary capillary circulation, while these alveoli continued to be ventilated

The next problem to consider is why there should be a cessation of flow through a portion of the pulmonary vascular bed? We made no measurements of the pressures in the pulmonary circuit during shock, and I have found few references on this subject From here on, I can

of hemorrhagic hypotension and second in the group which died Determinations were made during the control period *1* and *2* at 50 75 and 95 minutes of hypotension *3* *4* and *5* and one hour after the reinfusion of all reservoir blood *6*

In Table XVIII the individual values for each dog are shown for the six experimental periods You will notice that the mean values for all six periods do not differ significantly from each other However when the differences in each dog are followed during the experiment especially between columns 2 and 3 some values increase some remain unchanged while others actually decrease

Table XIX shows the results in the animals which died following

TABLE XVIII

Per Cent Oxygen Saturation of Arterial Blood in Dogs Which Survived 100 Minutes of Hemorrhagic Hypotension

PER CENT SATURATION OF ARTERIAL BLOOD SURVIVORS

| | 1 Control | 2 Control | 3 50 min | 4 75 min | 5 95 min | 6* |
|---|---|---|---|---|---|---|
| X 6 | 94 0 | 89 5 | 89 0 | | | 94 0 |
| X 3 | 91 0 | 93 0 | | | 95 0 | 98 0 |
| X 19 | 91 0 | 90 6 | 93 5 | 92 6 | 92 7 | 91 1 |
| X 21 | 91 4 | 91 6 | 88 3 | 89 2 | 92 9 | 91 3 |
| X 22 | 93 0 | 94 0 | 95 0 | 94 3 | 92 8 | 90 1 |
| X 24 | 80 6 | 93 5 | 94 0 | 95 2 | 94 5 | 88 9 |
| X 18 | 90 8 | 92 4 | 86 0 | 89 0 | 90 4 | 82 1 |
| Mean | 90 2 | 92 1 | 91 0 | 92 1 | 93 1 | 90 8 |

*One hour after reinfusion of all reservoir blood

only theorize Rounthwaite, Scott, and Gurd (5) from Montreal measured both pulmonary artery and pulmonary vein pressures in hemorrhagic shock and found no evidence of an increased pressure gradient Values for pulmonary arteriolar resistance were not given in their paper

However, many observers have noted that the lungs in hemorrhagic hypotension are dry and bloodless It has also been well documented that vasoconstriction develops in other vascular beds in shock, so it appears not unreasonable to suppose that vasoconstriction might also occur in the pulmonary vascular system

If vasoconstriction occurs during shock, and if the pulmonary arteriolar resistance is greater in certain areas of the lung than elsewhere in the lung, then "critical closure" of some part of the pulmonary vascular system might occur While I have made no measurements of critical closing pressure during shock, this concept appears, to me at least, to offer an explanation as to why the flow of blood to a certain portion of the pulmonary parenchyma might cease However, there may be other explanations for the cessation of flow

In summary, and working backward, the following sequence would be an hypothesis to explain some of my findings I stress this word hypothesis, since my data are incomplete During hemorrhagic shock, the pulmonary arteriolar resistance increases, and this is largely because of vasoconstriction of the pulmonary arterioles In some areas in the lung, this vasoconstriction will be more marked than elsewhere In these areas, the available pressure gradient necessary for the flow of blood through these vasoconstricted arterioles is insufficient, and these arterioles will "critically close" Thus the flow of blood through a portion of the pulmonary vascular bed will cease, while the alveoli in this portion of the lung continue to be ventilated As a result, no gas exchange will occur across the alveolar membrane and respiratory studies will show an increase in physiological dead space

## BLOOD OXYGEN STUDIES

The second group of observations that I would like to discuss concerns the values for per cent saturation of arterial blood which we found during shock It will be remembered that these anesthetized animals are hypoventilating during the control period, and their control per cent saturation therefore will be below normal However, during the hypotensive period of shock these animals are hyperventilating and one would expect an increase, above control values, in the per cent saturation of arterial blood

The next two tables show our values for per cent saturation of arterial blood, first in the group of seven dogs which survived 100 minutes

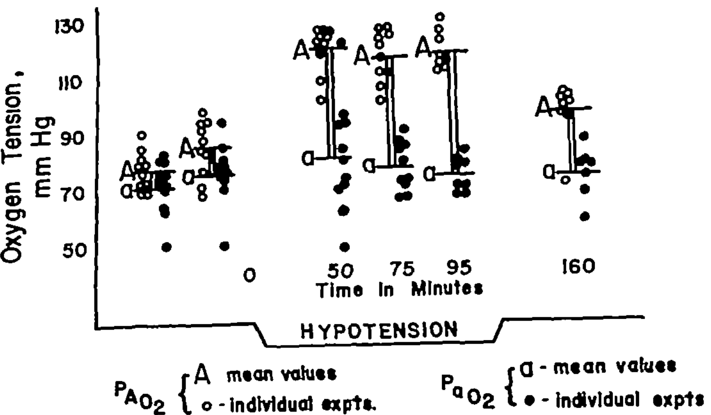



FIGURE 62 Alveolar and arterial oxygen tensions in eleven experiments with hemorrhagic hypotension Alveolar oxygen tension ($P_{A_{O_2}}$) calculated from the alveolar air equation using the the arterial carbon dioxide tension derived from the Henderson Hasselbalch equation Arterial oxygen tension ($P_{a_{O_2}}$) derived from oxygen dissociation curves. Five survivors and six fatalities

our procedure of administering shock stimuli Again we see the same type of response, the mean for all the animals shows that the per cent arterial saturation during shock does not change appreciably from control values However, some values during the hypotensive period have increased (especially dog X-11 in which the values increased from 81 to 99 per cent), in some dogs the values have not changed, while in others the per cent saturation has actually decreased during shock

When the thirty-three individual values for per cent saturation of arterial blood, obtained during the hypotensive period of shock, are

### TABLE XIX

**Per Cent Oxygen Saturation of Arterial Blood in Dogs Which Died Following Hemorrhagic Shock**

1 2 6

3 4 5

PER CENT SATURATION OF ARTERIAL BLOOD FATALITIES

| | 1 Control | 2 Control | 3 50 min | 4 75 min | 5 95 min | 6* |
|---|---|---|---|---|---|---|
| X - 10 | 91 5 | 91 7 | 82 8 | | 89 2 | 93 4 |
| X - 11 | 88 4 | 81 1 | 99 5 | 88 0 | 90 5 | |
| X - 12 | 90 6 | 89 3 | 86 0 | | | |
| X - 23 | 92 7 | 92 3 | 95 3 | 88 9 | | |
| X - 4 | 82 0 | 84 4 | 82 7 | | | 96 0 |
| X - 15 | 89 4 | 93 5 | 95 5 | 94 0 | 92 6 | 93 9 |
| X - 16 | 91 1 | 96 4 | 96 1 | 94 8 | | |
| X - 17 | 93 7 | 92 9 | 94 3 | 94 1 | | |
| Mean | 89 9 | 90 2 | 91 5 | 92 0 | 90 8 | 94 4 |

*One hour after reinfusion of all reservoir blood

The A A oxygen gradient returned toward normal values one hour after the reinfusion of all the reservoir blood

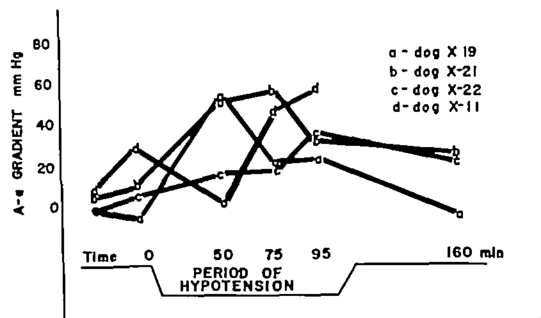



FIGURE 63 Alveolar arterial (A A) oxygen gradients in four experiments (three survivors one fatality) during hemorrhagic hypotension

Other workers in the past have measured the per cent saturation of arterial blood during shock Doi (6) in 1921 found no difference fol lowing hemorrhage in the cat However in 1943 Cournand Riley and Bradley (7) reported on their studies of the circulation in clinical shock and found normal values in four cases of hemorrhage

In 1944 Engel Harrison and Long (8) quoted Price (9) as saying that the per cent arterial saturation showed little change during shock except terminally Engel et al record data on one cat with a systemic blood pressure of 50 mm Hg in which the blood was 85 per cent satur ated and another cat with a blood pressure of 40 mm Hg in which the saturation was 90 per cent Wiggers (4) stated that neither anox emic or anemic anoxia occurred during the development of normovol emic shock

Other investigators have measured the hematocrit and the arterial oxygen content during shock and from such studies an idea of direc tional change in per cent saturation of arterial blood can be derived if certain factors are taken into consideration When hemodilution oc curs the hemoglobin hematocrit and oxygen capacity of the blood will be reduced and the hemoglobin and oxygen capacity will show parallel changes However the hematocrit changes may not exactly parallel the

grouped, eleven were less than 90 per cent and twenty-two were greater than 90 per cent Thus, in our experiments, regardless of whether or not the dog subsequently survived, the average per cent saturation of arterial blood showed little change during the course of hemorrhagic hypotensive shock

In eleven experiments, the alveolar and arterial oxygen tensions were calculated Figure 62 shows these individual values, their mean values, and the mean alveolo-arterial oxygen gradients before, during, and after 100 minutes of hemorrhagic hypotension The average alveolar oxygen tension increased from a control value of 81 mm Hg to 119 mm Hg at 50 minutes of hypotension, and remained elevated during the remainder of the hypotensive period The arterial oxygen tensions, on the other hand, changed very little during the experiment The average A-A gradients therefore show marked changes, rising from a control of 7 5 mm Hg to 39 mm Hg—the average of the hypotensive periods The gradient at one hour post reinfusion was 22 mm Hg

*Cournand* Are these figures based on the partial pressure of carbon dioxide in the blood?

*Merriman* I have calculated the alveolar oxygen tension ($P_{AO_2}$) from the alveolar air equation The value for the arterial tension of carbon dioxide ($PaCO_2$), derived from the Henderson-Hasselbalch equation, is substituted in the alveolar air equation

*Cournand* Are these determined from the standard dissociation curve?

*Merriman* Yes, the oxygen tension is derived from oxygen dissociation curves

*Cournand* I should be a little hesitant to measure gradients on the basis of these data

*Merriman* I agree, Dr Cournand, that these are not the best methods, but they were the only ones that were available

Figure 63 shows the values for the A-A gradients in four dogs It shows the variations in the same animal at different times during an experiment Dog X-22, shown in line *c*, for instance, had an oxygen gradient of 17 mm Hg at 50 and 75 minutes of hypotension, but at 95 minutes the gradient was 32 mm Hg In others, the gradient is large at 50 minutes of hypotension, while later in the hypotensive period it may become either larger or smaller Of the twenty-nine alveolar-arterial oxygen gradients determined during the hypotensive period of shock, seven were less than 30 mm Hg, and 22 were greater than 30 mm Hg This increased gradient was due to the markedly increased alveolar oxygen tension with the arterial oxygen tension changing little

The A A oxygen gradient returned toward normal values one hour after the reinfusion of all the reservoir blood

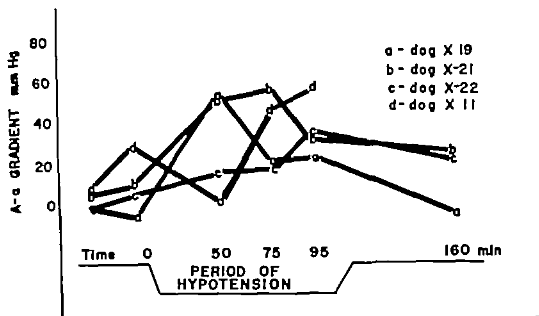



FIGURE 63 Alveolar arterial (A A) oxygen gradients in four experiments (three survivors one fatality) during hemorrhagic hypotension

Other workers in the past have measured the per cent saturation of arterial blood during shock Doi (6) in 1921 found no difference fol lowing hemorrhage in the cat However in 1943 Cournand Riley and Bradley (7) reported on their studies of the circulation in clinical shock and found normal values in four cases of hemorrhage

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hemoglobin changes The ratio of the hemoglobin to the hematocrit is the mean corpuscular hemoglobin concentration (M C H C ) and a change in this index has been shown in acute experiments to be an index of the movement of water in and out of the red cell (10, 11)

In our studies, we found that the M C H C changed only slightly during the hypotensive phase of hemorrhagic shock and the direction of the change was not always the same During the hypotensive period, the M C H C decreased on the average by only 2 per cent, and returned to slightly above control values at one hour post reinfusion For all practical purposes, therefore, the hemoglobin, hematocrit and oxygen capacity of the blood will change proportionately during hemorrhagic shock

Beecher *et al* (12), in a study of the "shock delaying" action of the barbiturates, presented values in thirteen dogs for hematocrit and arterial oxygen content during the control period and during hemorrhagic shock, under the conditions of ether with room air and sodium amytal with room air

Table XX shows their values for hematocrit, Hct, and arterial oxygen content, in the hemorrhage experiments with dogs anesthetized with sodium amytal and breathing room air From these values, I have calcu-

TABLE XX

Arterial Oxygen Content and Hematocrit in Hemorrhage Experiments (12)

| | Hematocrit | | Arterial $O_2$ Content Vols % | | Ratio $\frac{A_{O_2}}{Hct} \times 100$ | |
|---|---|---|---|---|---|---|
| Dog # | Control | Shock | Control | Shock | Control | Shock |
| 14 | 35 6 | 33 8 | 14 0 | 14 1 | 39 4 | 41 7 |
| 15 | 29 1 | 28 6 | 11 0 | 11 1 | 37 8 | 38 8 |
| 16 | 38 4 | 32 9 | 11 4 | 13 0 | 29 7 | 39 5 |
| 17 | 39 4 | 39 2 | 14 2 | 16 0 | 36 0 | 40 8 |
| 18 | 38 9 | 54 7 | 14 9 | 18 8 | 38 3 | 34 4 |
| 19 | 42 7 | 53 8 | 15 8 | 20 1 | 37 0 | 37 4 |
| 20 | 43 7 | 42 7 | 17 7 | 17 3 | 40 5 | 40 6 |

lated the ratio $A_{O_2}$/Hct x 100 If the hematocrit remained the same as for example in his dog 17 and the arterial oxygen content increased then this ratio will also increase signifying an increase in the per cent saturation of the arterial blood The following are the values for this ratio The first four dogs show an increase in the ratio dog 18 however, shows a drop in this ratio from 38 3 to 34 1 In the other two dogs this ratio does not change In Beecher s thirteen experiments the ratio $\frac{A_{O_2} \times 100}{Hct}$ during shock changed as follows an increase in 8 unchanged in 3 and a decrease in 2

Thus if the M C.H C. remained unchanged eight of his animals showed an increase in per cent saturation during hemorrhagic shock

## TABLE XXI

### Arterial Oxygen Content and Hematocrit (4)

| | | Control | OLIGEMIC SHOCK | | NORMOVOLEMIC SHOCK | | |
|---|---|---|---|---|---|---|---|
| | | | Early 30-min period | Critical stage | Compensatory stage | Progressive stage | Terminal stage |
| | $A_{O_2}$ | 8 8 | 8 7 | 9 5 | 10 9 | 11 7 | 11 1 |
| MT 11 | Hct | 21 0 | 21 0 | 21 0 | 26 5 | 27 0 | 25 0 |
| | $\frac{A_O}{Hct}$ | 41 8 | 41 4 | 45 1 | 41 2 | 43 3 | 44 4 |
| | $A_{O_2}$ | 12 9 | 15 5 | 14 1 | 14 5 | 15 5 | 15 5 |
| MT 14 | Hct | 30 0 | 37 0 | 37 0 | 33 5 | 39 5 | 36 0 |
| | $\frac{A_O}{Hct}$ | 43 0 | 41.8 | 38 1 | 43 2 | 39 2 | 43 0 |
| | $A_{O_2}$ | 19 6 | 18 2 | 18 9 | 23 5 | | 22 4 |
| MT 19 | Hct | 47 0 | 47 0 | 49 0 | 56 0 | | 51 0 |
| | $\frac{A_O}{Hct}$ x 100 | 41 7 | 38 7 | 38 6 | 42 0 | | 44 0 |

hemoglobin changes The ratio of the hemoglobin to the hematocrit is the mean corpuscular hemoglobin concentration (M C H C) and a change in this index has been shown in acute experiments to be an index of the movement of water in and out of the red cell (10, 11)

In our studies, we found that the M C H C changed only slightly during the hypotensive phase of hemorrhagic shock and the direction of the change was not always the same During the hypotensive period, the M C H C decreased on the average by only 2 per cent, and returned to slightly above control values at one hour post reinfusion For all practical purposes, therefore, the hemoglobin, hematocrit and oxygen capacity of the blood will change proportionately during hemorrhagic shock

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|---|---|---|---|---|---|---|
| Dog # | Control | Shock | Control | Shock | Control | Shock |
| 14 | 35 6 | 33 8 | 14 0 | 14 1 | 39 4 | 41 7 |
| 15 | 29 1 | 28 6 | 11 0 | 11 1 | 37 8 | 38 8 |
| 16 | 38 4 | 32 9 | 11 4 | 13 0 | 29 7 | 39 5 |
| 17 | 39 4 | 39 2 | 14 2 | 16 0 | 36 0 | 40 8 |
| 18 | 38 9 | 54 7 | 14 9 | 18 8 | 38 3 | 34 4 |
| 19 | 42 7 | 53 8 | 15 8 | 20 1 | 37 0 | 37 4 |
| 20 | 43 7 | 42 7 | 17 7 | 17 3 | 40 5 | 40 6 |

mately 15 to 20 per cent of the cardiac output would have to be shunted to explain these differences assuming A V $O_2$ difference of 5 volumes per cent

Berggren (15) found an 11 mm A A oxygen gradient in subjects breathing pure oxygen Assuming a normal arteriovenous oxygen difference he concluded that 0 6 per cent of the circulating arterial blood was of venous origin It appears therefore that the A A gradient for oxygen in normal dogs breathing room air is mainly caused by the uneven distribution of inspired air Our mean control A A gradient of 7 5 mm Hg would be in agreement with these observations Whether or not there is a small amount of venous admixture to arterialized blood in normal dogs is a point worthy of discussion

To test the hypothesis of venous admixture to arterialized blood an additional five experiments were made in June 1954 The same method of inducing shock was used although the hypotensive level was slightly higher 48 mm Hg The dogs were given 100 per cent oxygen to breathe for 7 and sometimes 15 minutes before an arterial sample of blood was withdrawn for analysis of oxygen content and hemoglobin These samples were obtained during the control period at frequent intervals during the hypotensive period and again after the reinfusion of all the reservoir blood All samples were analyzed immediately From the hemoglobin determination the value for 100 per cent saturation was obtained The difference between the arterial oxygen content and this value for 100 per cent saturation represents the volume of dissolved oxygen.

Table XXII shows our results for the amount of dissolved oxygen in volumes per cent at the various time periods During some control and post reinfusion periods a second arterial sample was obtained after the subject had inspired pure oxygen for 15 minutes The volume of dissolved oxygen is calculated by subtracting the value for 100 per cent saturation, determined from the hemoglobin content from the value for the arterial oxygen content

It will be noted that the volume of dissolved oxygen after 15 minutes of 100 per cent oxygen breathing was less than that at 7 minutes This occurred in six out of seven instances most of which were during the control period In dog X 26 the control values for dissolved oxygen are in the neighborhood of 1 2 volumes per cent The values at 95 minutes of hypotension, and after the reinfusion of blood, are considerably higher than during the control period Although the control bloods clotted in dog X 27 the post infusion values are again greater than the average control values It will be noted however that during the hypotensive period of shock, the values for dissolved oxygen vary some

three showed no change, and two animals showed a decrease in per cent arterial oxygen saturation during shock

Wiggers, in his book, "Physiology of Shock" (4), presented values in five dogs, for hematocrit and oxygen content, during the course of hemorrhagic shock I have calculated the ratio $A_{O_2}$/Hct x 100 and the data for three of his dogs are shown in Table XXI In dog MT 11, the ratio remained unchanged during the early 30-minute period of hypotension and then increased during the critical period of oligemic shock During normovolemic shock, the ratio decreased and later increased again to above the control value In dogs MT 14 and MT 19, the ratio showed a progressive fall during oligemic shock, and increased to or above control values during normovolemic shock

It appears that in some of Wiggers' experiments, there was no change in per cent arterial saturation, in some there was an increase, but many determinations showed a value for calculated per cent saturation of arterial blood below control values These findings, therefore, are similar to our own

The question which now arises is What is the explanation for the marked degree of arterial oxygen unsaturation and the large A-A gradient which develops in some animals during the hypotensive period of shock?

The A-A gradient found in the normal dog breathing room air is believed to be caused chiefly by the uneven distribution of inspired air into the different alveoli of the lung (13, 14) As a result, some alveoli will be underventilated, and some hyperventilated The net effect because of the shape of the $O_2$ dissociation curve will be that the value for arterial oxygen tension will be lower than that which would exist if all alveoli had the same oxygen tension By gradient studies, a diffusional barrier to oxygen transfer has been shown not to exist in the normal dog's lung, during the inspiration of 12 to 15 per cent oxygen

The other factor which must be considered in explaining an A-A gradient is whether or not venous blood enters the arterial circulation without undergoing gas exchange This is referred to as venous admixture Williams (14) observed that when dogs were given pure oxygen to breathe, there was, at the most, only a small difference between alveolar and arterial oxygen tensions He went on to say that if the gradient of 14 mm Hg, which he observed during the breathing of room air, was caused by venous admixture to arterialized blood, a gradient of 100 mm Hg would result during the inspiration of 100 per cent oxygen

Suskind (13) stated that if the direct shunting of venous blood alone were responsible for the gradient while breathing room air, approxi-

mately 15 to 20 per cent of the cardiac output would have to be shunted to explain these differences assuming A V O difference of 5 volumes per cent

Berggren (15) found an 11 mm A A oxygen gradient in subjects breathing pure oxygen Assuming a normal arteriovenous oxygen difference he concluded that 0 6 per cent of the circulating arterial blood was of venous origin It appears therefore that the A A gradient for oxygen in normal dogs breathing room air is mainly caused by the uneven distribution of inspired air Our mean control A A gradient of 7 5 mm Hg would be in agreement with these observations Whether or not there is a small amount of venous admixture to arterialized blood in normal dogs is a point worthy of discussion

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## TABLE XXII

### Volume of Dissolved Oxygen (in Volume Percentage) in Arterial Blood Under Varying Circumstances

| | | X - 26 | X - 27 | X - 28 | X - 29 | X - 30 |
|---|---|---|---|---|---|---|
| Control | 7 | 1 21 | | 1 25 | 1 10 | 1 09 |
| | 15 | 1 26 | | 1 04 | | |
| | 7 | 1 16 | | 1 11 | 1 05 | 1 38 |
| | 15 | 99 | | 73 | | |
| | 10 | 1 16 | 95 | 1 21 | 1 39 | 1 04 |
| Minutes | 20 | | | | 55 | 35 |
| of | 30 | 38 | 09 | — 05 | 1 13 | 1 30 |
| Hypo- | 50 | 92 | 1 06 | 42 | 72 | 99 |
| tension | 75 | 1 02 | 1 05 | 45 | 73 | |
| | 95 | 1 97 | 76 | 78 | 75 | 1 27 |
| Minutes | 10 | | | | 1 33 | |
| Post | 30 | 1 70 | 1 82 | 10 | 79 | |
| Reinfusion | 60 | 2 18 | 1 83 | 23 | 1 18 | 1 01 |
| | | 1 75 | 1 59 | — 19 | | |

times they are not different from the control values, while at other times there are one or two values for each dog which are definitely below control values You will note that in all dogs, the value for dissolved oxygen at the 10-minute period of hypotension is not significantly different from the control value This fluctuation in the amount of dissolved oxygen is similar to the trend in calculated per cent saturation of arterial blood seen in Dr Wiggers' data (Table XXI) On reviewing this data, I have no definite explanation for the arterial oxygen unsaturation that was present in some animals during the hypotensive period of shock or for the reduced values for dissolved oxygen However, I raise the question whether this could result from venous admixture, possibly through pulmonary arteriovenous fistulas

*Nickerson* In your method a very small error in total oxygen content determination would produce a big percentage difference in the amount of dissolved oxygen

*Merriman* That is correct Theoretically the amount of dissolved oxygen present in a sample of blood after breathing 100 per cent oxygen would be 0 003 volumes per cent per mm $P_{O_2}$ In our experiments the alveolar oxygen tension would be approximately 660 mm Hg at this tension the amount of dissolved oxygen should have been 2 0 volumes per cent For some reason or another I found only 1 2 volumes per cent Preston and Ordway (16) found 1 2 volumes per cent in normal children My reasoning had been that if venous admixture did occur during shock the arterial oxygen content would be reduced and we believed that our Van Slyke technic could detect this decrease as a significant figure

*Cournand* May I ask you whether you measured the oxygen capacity at any point during the study?

*Merriman* Only as checks on the study

*Cournand* But you are basing the capacity on the hematocrit aren t you?

*Merriman* No I am basing the oxygen capacity on the hemoglobin determination Before the commencement of these experiments a series of hemoglobin contents obtained from Van Slyke oxygen capacity determinations was calibrated and checked against the hemoglobin contents of the same sample of blood using the King cyan hematin method (17)

*Nickerson* You must assume that the hemoglobin and plasma both come to equilibrium with the partial pressure of oxygen in a particular sample, irrespective of how they may have come into your original sample as venous or arterial blood

*Merriman* That is right

*Nickerson* One thing that bothers me is the basis for the very low dissolved oxygen values in blood that is equilibrated with hemoglobin which is essentially saturated

*Cournand* May I make certain that in every instance where you have an oxygen content, you have measured also an oxygen capacity?

*Merriman* No

*Cournand* Since the dogs are in shock the hematocrit might vary and therefore the $O_2$ capacity will also vary

*Merriman* I must make myself clear on this point Before starting these experiments the hemoglobin content determined by the King method was calibrated to give the same value as the hemoglobin content determined from the Van Slyke oxygen capacity analysis Then during

every experiment, each sample of arterial blood was first analyzed for its oxygen content and then duplicate hemoglobin contents were determined on this same sample of blood Thus, this hemoglobin content would give the same value as an oxygen capacity determination

*Cournand* You had a hemoglobin on each of them?

*Merriman* Definitely, duplicate hemoglobins were done

In 1940, Wood, Mason, and Blalock (18) studied in five dogs the effect of the inhalation of pure oxygen in experimental shock produced by hemorrhage In their Table I, they give values for oxygen capacity and oxygen content in volumes per cent The mean per cent oxygen saturation 118 minutes after the first bleeding was 88 4 per cent After 15 minutes of inspiring pure oxygen, the arterial blood had not become fully saturated

Similarily, in their experiments with shock produced by histamine and by trauma, the blood after 15 minutes of oxygen breathing was not completely saturated

*Cournand* Is it not true, Dr Richards, that in the hundreds of human patients we have seen we have never observed, except in those with thoracic injuries, any similar reduction in oxygen content?

*Richards* I think in animals depleted as much as this there might be atelectatic regions of the lung that would come and go very rapidly with secretions developing, and so on, that might offer regions for a passage of blood through unaerated channels

*Cournand* Then they are under anesthesia

*Merriman* These animals were anesthetized Venous admixture could occur for many reasons, and one explanation might be that certain alveoli are perfused, but are underventilated There is some confusion as to whether pulmonary alveolar edema actually develops during shock Unfortunately, we made no miscroscopic studies of the lungs in shock, but it is our impression that during the hypotensive period of shock, the lungs are dry and bloodless Eaton (19) found histopathological changes in the lungs which developed within 10 to 20 minutes after an acute hemorrhage which amounted to 25 per cent of the blood volume These changes consisted of edema, congestion, and hemorrhage which were usually of a spotty nature He found that there was an abrupt increase in alveolar edema at 10 minutes following blood loss, a lesser degree at 20 minutes, and a negligible amount at 45 minutes After this, there was a definite trend to a reaccumulation of edema, reaching a peak at 72 hours, when this edematous condition was marked

Moon (20), however, stated that the lungs in hemorrhagic hypotension are characterized by pallor and dryness Dr Wiggers, in his book, "Physiology of Shock" (4), stated that in 430 necropsies "Pulmonary

edema was only occasionally noted and in these instances a strong suspicion of some antecedent pulmonary condition usually existed Likewise areas of congestion are not uncommon in the adrenal cortex and lungs of stray dogs hence their occasional occurrence in shock may be coincidental

*Cournand* As pulmonary edema is not observed in either anesthetized animal or in man in shock, your premise is it seems to me a highly artificial one

*Merriman* I have wondered whether or not pulmonary edema occurs You will notice that these marked changes do not occur in every animal and this is borne out by the studies by Beecher (12) and by Wiggers (4) It may be that it occurs only in the more severe grades of shock In my experiments the cardiac output was reduced during shock to 22 per cent of the control value

*M Knisely* How many separate phenomena might be listed which would create an underventilated state marked retention in the alveoli pulmonary edema What else might we list?

*Merriman* First of all the distribution of inspired air into the different alveoli may not be uniform with the result that the ventilation/perfusion ratios in different parts of the lung are differerent This is the main reason for the gradient found in our dogs during the control period and also explains the gradient in man, when breathing room air Secondly there may be a diffusional barrier to the transfer of oxygen from the alveoli to the pulmonary capillary blood which in this case would have to develop during shock. Finally venous blood may enter the arterial blood unaltered and it may do so in many ways

Butterworth (21) has demonstrated that coronary venous blood enters the left atrium in the normal dog

Venous admixture will result from perfusion of unventilated alveoli as for example in pulmonary edema or in the presence of atelectasis Venous admixture could also occur if blood flowed through pulmonary arteriovenous fistulas or through shunts In 1702 Cowper wrote on viewing the extremities of the pulmonick blood vessels in a living frog with my microscope I found their communications much larger than those that I had before seen in the membrane between the toes and in the feet of the same creature (22)

More recently arteriovenous shunts in the lung have been suspected to explain the passage of certain parasites through the lung and to explain those puzzling cases of paradoxical emboli It is also known that arteriovenous aneurysms do occur in the lung in cases of hereditary hemorrhagic telangiectasia (23 24 25)

In 1948 Prinzmetal and his associates (26) using glass spheres

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mained unchanged in only three experiments In five experiments the physiological dead space was definitely increased during the hypotensive period of shock

*Barcroft* I have in mind experiments performed by Peter Daniel and his group (31) on animals in severe shock Roentgen ray opaque materials were given intravenously and serial photographs were made of the entry and spread of these materials through different organs This was done in the kidney the liver and the lungs In particular in the lungs in some animals in severe shock they found that the arterial blood never got to the outer parts of the lungs Might that not perhaps be connected with this apparent increase in dead space?

*Merriman* Definitely *If the physiological dead space increases* it means that an additional portion of the tidal volume has not undergone gas exchange It means that some alveoli continue to be ventilated but not perfused This nonperfusion may be because of vasoconstriction or some other reason

*Barcroft* Yes Dr Daniel was very careful to avoid the mechanism and to concentrate simply on demonstrating the fact that it occurred

*Cournand* May I amend my previous statement on the diffusing capacity? If there is a very marked reduction in the alveolar-capillary interface, related to a reduced pulmonary flow with part of the capillary system being closed off as a result of the effects of the closing pressure then the diffusing capacity would be reduced The situation in shock requires more study with direct measurements of the A A gradients

*Merriman* I agree entirely

*Cournand* In other words a measurement of oxygen tension rather than saturation

*Merriman* When I did this work at the University of Western Ontario these were the only methods that were available I fully realize the limitations of my methods and my conclusions can be regarded only as theories which are open for discussion

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demonstrated arteriovenous shunts larger than capillaries in the lungs of certain animals In 1950, Tobin and Zariquiey (27) verified this work by using the glass sphere technic followed by latex injection media This anatomical study showed that arteriovenous shunts, from 25 to 500 μ in diameter were present in isolated human lungs with little or no pulmonary pathology

In 1952, Rahn, Stroud, and Tobin (28) again demonstrated A-V shunts in the lungs of normal dogs, by cinefluorography In addition, in one dog, several glass spheres 200 μ in diameter were injected into the pulmonary artery Three seconds later a sample of aortic blood was withdrawn and was found to contain one glass sphere Injection studies later revealed the presence of an arteriovenous shunt in this dog's left lung

On the other hand, Gordon (29), using different methods, was unable to find pulmonary arteriovenous vessels larger than 25 μ in internal diameter Similarily, Miller (30) makes no mention of these vessels in the lung

In summary, I have no definite explanation for the arterial oxygen unsaturation which is found in some animals during shock I think that there is a small A-A gradient both during the control period and during the hypotensive period of shock which is due to variations in the ventilation/perfusion ratio

However, to explain the large A-A gradients or the marked degree of arterial oxygen unsaturation, some form of venous admixture must be considered Of the possibilities listed above, I do not believe, from Butterworth's work (21), that enough coronary venous blood could enter the left atrium to account for these changes The explanation, therefore, must be between perfusion of unventilated alveoli and pulmonary arteriovenous shunts

*Cournand* Alveolar $O_2$ tension in human shock is most likely normal In order for a diffusion gradient to become apparent, while breathing room air, it would be necessary to assume a considerable reduction in alveolar $O_2$ tension In subjects with alterations of the diffusion membrane, a reduction of the oxygen diffusing capacity only becomes apparent when inspired gas $O_2$ tension is lowered So I do not believe that diffusion has any effect here

*Merriman* I would concur

*Cournand* Of course, to follow through this problem would require a very extensive study of pulmonary function

*Barcroft* Am I right in thinking that in these animals sometimes the total dead space apparently increases?

*Merriman* Yes The values for the physiological dead space re-

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tocrit cardiac output systemic blood pressure and heart rate and in some subjects total body oxygen consumption For measuring cardiac output a 40- to 50-cm plastic tube was passed through the basilic arm vein and Evans blue dye was injected through it The dye-dilution curve was recorded continuously with a recording densitometer (1 2) connected to a radial artery needle With this device cardiac output could be measured accurately and repeatedly in the presence of saturated or unsaturated blood (3) Heart rate and mean systemic blood pressure were determined by a strain gauge connected to the same radial artery and total body oxygen consumption was quantitated by means of a Douglas bag and Scholander apparatus After these determinations the treadmill was started and adjusted at a rate (from 4 to 7 miles per hour) duration (from 3 to 10 min ) and grade (11 or 20 per cent) that would give a heavy and in some cases a maximum external work load

Natives at the high altitude were much smaller averaging 58 kg and 1 6 m$^2$ as compared to the subjects at sea level who averaged 68 kg and 1 8 m$^2$ In the natives the hemoglobin varied from 17 7 to 24 3 with an average of 20 2 gm /100 ml Their hematocrits averaged 60 with high and low values of 72 and 51 In the subjects measured at sea level the hemoglobin averaged 16 1 and the hematocrit 46 Some natives that we could not persuade to exercise on the treadmill had hematocrits of 85 They were ambulatory

In Table XXIII are presented the average calculated data on these human subjects The control data on subjects at sea level and at the high altitude are in some instances rather high but are not regarded quite the same as those from subjects at standing rest, since many were excited and stimulated by the unfamiliar procedures and the presence of strange personnel However I am inclined to accept the previous observations of Dr Rotta (4 5) that the native of a high altitude who has been studied at a high altitude and who has high hematocrit and hemoglobin values has a resting heart rate systolic and diastolic blood pressure oxygen consumption systemic arteriovenous oxygen difference and cardiac output (Fick procedure) which approximate those values of the sea level dweller who has been measured at sea level Dr Rotta also has some excellent pressure curves to show that in contrast to the normal values for the systemic circuit, the systolic pressure in the right ventricle and pulmonary artery is significantly elevated

The natives studied at the 15 000-ft elevation of Morococha have been separated into two groups according to their external work load stress The treadmill levels of work in these two groups ranging from 490 to 580 kg m /min /m.$^2$ (average 535) and from 650 to 749 kg m /min /m.$^2$ (average 697) are considerably less than the work loads at

# THE AORTIC AND CORONARY BLOOD FLOW

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I WOULD LIKE to discuss with you problems in the control of the blood flow through the aortic lumen and through the coronary arteries For a number of years I have been interested in a means of estimating the ability of the heart to perform A first approach to the problem is the determination of the maximum cardiac response in stress The following observations were made with normal men and dogs as subjects, and the presenting stresses were maximum treadmill exercise in man at sea level, maximum treadmill exercise in man with the additional stress of chronic anoxia at high altitude, and massive blood infusions in normal dogs and dogs with artery-vein fistulas We will consider briefly the *initiating, sustaining, and limiting factors which control the* work response of the heart Only the left ventricle will be considered

## VENTRICULAR RESPONSES TO EXERCISE AND ANOXIA

Studies on the response of the left ventricle of man to the stress of exercise and chronic anoxia were undertaken in Peru in September 1953 I should stress that this study was not a field trip Through the kindness of the Peruvian Government and especially Dr Hurtado and Dr Rotta of the Institute of Andean Biology, the facilities of two excellent and well equipped modern laboratories were made available to us, one in Lima and the other in the mining town of Morococha

Twenty-six male volunteer subjects were studied at Lima, Peru (elevation 500 ft ) and at Morococha, Peru (elevation 15,000 ft ) Those at Lima were volunteer medical students from 22 to 28 years old who were native to low altitudes Subjects at Morococha were natives of that region who had not lived at significantly lower regions, and who were healthy, active, and engaged in mining activities Their ages varied from 19 to 38 years

For control or reference measurements, the subjects stood on a motor-driven treadmill and determinations were made of hemoglobin, hema-

groups during exercise the highest pressures being 164 in a native at the high altitude and 122 in a medical student at sea level An occasional subject in each group showed no change or a slight reduction in mean blood pressure the average mean radial pressures during exercise for the natives of high altitude and subjects at sea level were 119 and 109 mm Hg respectively

At the lower level of treadmill exercise in the native at high altitude (average 535 kg m /min /m²) the average cardiac index (C I ) of 7 5 and cardiac work index (C W I ) of 12 3 are quite high the stroke volume index (S V I ) of 49 and stroke work index (S W I ) of 79 are not particularly increased The increase in cardiac output is caused largely by the heart rate change and not from a change in stroke volume Similarly augmentation of cardiac work is affected by a combination of the large increase in heart rate and a small increase in mean systemic blood pressure However the rise in cardiac work is probably somewhat less than indicated here This value must be corrected for any increase in end-diastolic pressure in the left ventricle during exercise Although we do not have any direct measurements of this pressure still from our experience in exercising dogs in which this pressure is considerably increased (6) we would be led to expect its augmentation in man

These values in the native exercising at high altitude compare with those of the medical students exercising at sea level despite the fact that the sea level dweller is exercising at a much heavier external work load (average 810 kg m /min /m²) Again the increased cardiac output and cardiac work were effected primarily by the increased heart rate

In the group of natives who exercised more strenuously at an average of 697 kg m /min /m² the cardiac index and cardiac work index are increased much further averaging 13 7 and 23 4 respectively Although the heart rate tends to be higher in this group not all of the increase in cardiac output and cardiac work is related to the change in heart rate and the mean systemic blood pressure change At this level of cardiac activity in addition, a significant portion of the increase in cardiac output and cardiac work arises from a sizable augmentation of stroke volume and stroke work

*Lamport* Do you happen to know if there was a change in the viscosity of the blood?

*Gregg* During the exercise period in the natives at the high altitude?

*Lamport* Yes, or change from one altitude to another?

*Gregg* These natives were studied only at the high altitude I do not know whether during the exercise there was any change in their viscosity Would you expect one?

*Lamport* I am not sure what would happen I do not know

TABLE XXIII

Treadmill Exercise (kg-m/min/m²) in Human Subjects at Sea Level and at High Altitude

| Condition | Stress kg-m/ min/m² | Heart Rate | Syst M B P mm Hg | C I l/ min | C W I kg-m/ min m² | S V I ml/ min m² | S W I gm m min m² | $O_2$ Usage l min/m² | A-V $O_2$ ml/ 100 ml |
|---|---|---|---|---|---|---|---|---|---|
| Morococha | | | | | | | | | |
| Rest | --- | 83 | 101 | 1 2 | 6 0 | 51 | 72 | 0 209 | 5 7 |
| Exer | 535 | 156 | 118 | 7 5 | 12 3 | 49 | 79) | 1 072 | 13 9 |
| Exer | 697 | 172 | 121 | 13 7 | 23 4 | 80 | 135) | | |
| Max Exer | 695 | 175 | 125 | 15 2 | 26 4 | 88 | 152 | ---- | --- |
| Lima | | | | | | | | | |
| Rest | --- | 81 | 92 | 2 8 | 3 6 | 33 | 41 | ---- | --- |
| Exer | 810 | 163 | 109 | 8 1 | 12 1 | 51 | 75 | 1 353 | 16 9 |
| Max Exer | 858 | 180 | 110 | 8 7 | 12 9 | 49 | 72 | ---- | --- |

sea level which ranged from 704 to 986 kg m/min /m² (average 810)

In all subjects, except for one native in the mountains and one medical student at sea level, the increase of the heart rate was large during exercise Increases in rate tended to be greatest with the greatest treadmill activity, the average heart rates for the two groups were 161 and 163 In contrast to the large increase in heart rate, the increase in mean systemic blood pressure (Syst M B P ) was generally mild in these

groups during exercise the highest pressures being 164 in a native at the high altitude and 122 in a medical student at sea level An occasional subject in each group showed no change or a slight reduction in mean blood pressure the average mean radial pressures during exercise for the natives of high altitude and subjects at sea level were 119 and 109 mm Hg respectively

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*Lamport* Do you happen to know if there was a change in the viscosity of the blood?

*Gregg* During the exercise period in the natives at the high altitude?

*Lamport* Yes or change from one altitude to another?

*Gregg* These natives were studied only at the high altitude I do not know whether during the exercise there was any change in their viscosity Would you expect one?

*Lamport* I am not sure what would happen I do not know

*Stead.* Short periods of heavy work cause a rise in hematocrit reading

*Gregg:* Following blood infusion in the dog and man a significant rise in the hematocrit generally occurs

*M. Kinsely:* One reason the hematocrit will rise is because small blood vessels in muscle leak fluid after the exercise or after each contraction

*Gregg* It is to be hoped that the hematocrit does not increase too much with exercise in these natives at the high altitude because they are already laboring under a heavy hematocrit burden from the effect of chronic anoxia

*Montgomery* Perhaps you have measurements of the average difference in the viscosity of blood at the two levels?

*Gregg* No, we have no measurements of them They have been made but I do not recall the figures

*Richards* You have no idea what their arterial oxygen saturations were in work at high altitude?

*Gregg* We have only occasional observations, which were around 80 per cent during exercise

*Comnand* These figures impress me by the very marked increase in oxygen uptake that there must be

*Gregg* These are the people who, as far as I am concerned, are not at the high altitude

*Comnand* So you did not take these figures to indicate that at the higher altitude they have a larger output?

*Gregg* No, I think I would accept Dr Rotta's figures (4, 5) on these nonworking subjects native to, and studied at, the high altitude In his series of catheterized subjects the cardiac index was about 2 8, arterial saturation 81, heart rate 68, hemoglobin 21, cardiac work index 4, and so on Of course, these subjects did have an elevated pulmonary artery pressure

*Green* Did the Lima group, the medical students, have normal hematocrits?

*Gregg:* Yes, I have the data here The average hematocrit approximated 48, the hemoglobin 16 gm /100 ml of blood

*Comnand* The response of a patient with chronic anoxia is certainly quite different from the response to acute anoxia Here, in so far as pulmonary pressure is concerned, there would be a resemblance, but with acute anoxia and bronchial disease there is an increase in hematocrit The normal output you mention is certainly something which is very strikingly different

*Gregg* Yes, we went to the mountains of Peru with the full intention of making measurements of pulmonary artery pressure and cardiac out-

put in these catheterized people at rest However Dr Rotta s pressure curves and flow measurements were excellent, and I saw no particular reason to repeat them

*Cournand* What was the heart rate of those subjects?

*Gregg* The average was about 68

*Cournand* They also adapt their rate because in acute anoxia with that same degree of unsaturation there would be a much more rapid rate wouldn t there?

*Gregg* That is true

*Bing* These figures are quite different from the original ones collected by Sir Joseph Barcroft (7) are they not? There was an increased cardiac output as far as I remember because it was used to explain some of the maintenance of mean capillary pressure at high altitude Of course the difference in methods is very striking

*Gregg* Although attempts were made to stress the left ventricle to a maximum work effort we are not sure whether or not this was accomplished either in the mountains or at sea level The data in Table XXIII for five natives of the high altitude have been selected as suggestive of maximum left ventricular effort Each of these subjects stated at the end of exercise that he was very tired or completely exhausted In these five individuals at the higher levels of treadmill work (650 to 749 kg-m /min./m² average 695) the cardiac work index was quite high ranging from 18 1 to 46 4 and averaging 26 4 kg-m /min /m Similarly in those medical students at sea level who were working at a considerably higher level of treadmill exercise (average 858) and who also claimed to be very tired cardiac work index ranged from 11 4 to 15 1 and averaged 12 9 kg-m./min /m² The so-called maximum values for these two groups are 15 to 20 per cent higher than the averages for the nonselected groups in Table XXIII

I take this to mean that although the hearts of these natives are well adapted and perform in the mountains with great ease yet with a comparable amount of external work their hearts respond with a greater effort than do the hearts of the native sea level dwellers when exercising at sea level

I should like to add a word about the calculation of the systemic arteriovenous oxygen difference at rest and during exercise in those instances in which both cardiac output and oxygen consumption were measured Such values are obviously only an approximation, since data for cardiac output and oxygen consumption are based on quite different time intervals However they should represent trends The control data in the mountain native for the calculated arteriovenous oxygen difference averaged 5 7 ml /100 ml during exercise this increased to

13.9 ml./100 ml. In the medical students exercising at sea level and at a somewhat greater intensity of treadmill work, the average calculated arteriovenous oxygen difference was 16.9 ml./100 ml. The values reported here during exercise are in the same range as those calculated by Asmussen and Nielsen (8) using the dye-dilution technic, and as those reported by Donald, *et al.* (9), in which the arteriovenous oxygen difference was determined directly with the Fick procedure.

These values are of interest in the light of the observations made yesterday about the tendency for the arteriovenous oxygen differences to be somewhat fixed in some of the vascular beds. I believe Dr. Bing indicated that the extraction of oxygen from the coronary bed was a fixed quantity except for the condition of congestive failure. I also had the same impression from Dr. Myers' data. However, this does not appear to be so for mixed venous blood during exercise. This raises the question as to what happens first in the peripheral beds of the various organs. Does the body early in a stress situation take advantage of the potentially high arteriovenous oxygen difference which is available (excluding now the heart) and extract most of the available oxygen or do the peripheral beds open up first and permit a large blood flow before the arteriovenous oxygen difference changes significantly? There is nothing in the data presented to indicate which of these early compensatory mechanisms is used, but the end result is certainly a very large average extraction. This probably means that in some of the peripheral vascular beds there is almost complete extraction, since the average extraction is a mean of many beds.

*Baez:* Can you tell us something concerning the comparative nutritional states of the native subjects at Morococha and of the medical students in Lima? Also I should like to ask whether test runs with the same sample at high altitudes and at sea level are comparable? In other words, is it possible for the equipment of the observers to be affected by the altitude?

*Gregg:* My impression was that the nutritional state of the subjects in Morococha was somewhat better than that of the sea level subjects. The people in the mountains appeared to be in excellent condition. They were thin individuals with an emphysematous type of chest except for one or two who were drivers of station wagons for the laboratory and who had accumulated a certain amount of fat. Most of them, however, played considerable soccer and were quite active physically.

## MAXIMUM CARDIAC OUTPUT AND WORK DURING MASSIVE BLOOD INFUSIONS

I should now like to proceed with some observations on attempts to

measure maximum cardiac output and work induced in the anesthetized closed-chest dog by means of massive intravenous blood infusions (10 11) In this instance the increase in cardiac output and cardiac work arises from the increased venous return and increased blood volume created by infusion This contrasts with the situation in the exercising subject in whom the increased venous return arises from the activity and excitement of the individual Cardiac output was determined with the dye-dilution method (1 2) Evans blue dye being injected into a catheter in the external jugular vein with the tip near the right atrium and continuous sampling was made from a previously constructed ca rotid loop connected to the recording densitometer Effective left ven tricular end-diastolic pressure was obtained from the left ventricular pressure curve by needling a previously prepared cardiopexy and from the intrapleural pressure simultaneously recorded

After control measurements of pressures heart rate and cardiac out put fresh heparinized cross matched blood at near body temperature was infused into a leg vein at rates from 2 to 7 ml /min /kg and deter minations of pressure and flow made periodically thereafter Maximum cardiac work response was taken as the point where with continued in fusion cardiac work started to decrease

In Table XXIV are the average data for a large number of normal and arteriovenous fistula dogs In the normal anesthetized dog after be ing infused (stress) an average of 1430 ml of blood in 38 minutes the cardiac index, cardiac work index stroke volume index and stroke work index increase greatly reaching average values of 6 3 8 9 49 and 71 respectively The heart rate is elevated much less and the systemic blood pressure much more than in the exercising human subject However the effective mean blood pressure (systemic mean blood pressure—effective left ventricular end-diastolic pressure (Eff L V E D P)) is only slightly increased since with infusion the end-diastolic pressure is greatly ele vated I think the general conclusion can be drawn that the increased cardiac output and cardiac work were effected largely by an increased stroke volume and stroke work and only mildly by the increased heart rate and blood pressure which did not change greatly This mechanism of response contrasts with that observed in the exercising human subject

To study further the maximum cardiac work response the hearts of normal dogs were subjected for long periods of time to the increased stress of a large chronic arteriovenous fistula and the cardiac response was then re evaluated before and during acute hypervolemia A num ber of aortacaval fistula dogs were studied in this way 2 to 3 months postoperatively The dogs with aortacaval fistulas exhibited various manifestations of a heavy cardiovascular load such as moist rales as

TABLE XXIV

Blood Infusion in Normal and Fistula Dogs

| Condition | Stress | Heart Rate | Syst M B P mm Hg | Eff L V E D P mm Hg | C I l/min | C W I kg-m/min/m² | S V I ml/min/m² | S W I gm m/min/m² |
|---|---|---|---|---|---|---|---|---|
| Normal | | | | | | | | |
| Rest | --- | 102 | 100 | 7 | 2 0 | 2 5 | 25 | 31 |
| Inf 38′ | 1430 ml | 123 | 150 | 34 | 6 3 | 8 9 | 49 | 71 |
| A-V Fistula | | | | | | | | |
| Rest | --- | 134 | 86 | 26 | 8 8 | 7 1 | 64 | 52 |
| Inf 11′ | 178 ml | 144 | 86 | 26 | 8 9 | 6 9 | 65 | 48 |
| Periph Fist | | | | | | | | |
| Rest | --- | 103 | 98 | 11 | 7 1 | 8 6 | 71 | 86 |
| Inf 25′ | 1145 ml | 110 | 132 | 28 | 8 0 | 11 3 | 73 | 103 |

cites, peripheral edema, and increased weight during the postoperative observation period Dogs prepared with multiple peripheral fistulas (bilateral iliac or iliac-femoral fistulas) remained healthy for 24 months and showed none of the external signs of circulatory strain exhibited by the group with a central fistula

The control values for cardiac index, cardiac work index, stroke volume index, and stroke work index in the dogs with aortacaval fistulas before infusion approximate those in the normal dogs after maximum

cardiac work response had been obtained with blood infusion These control hemodynamic levels represent either a maximum left ventricular work response or something less than this since without exception cardiac work failed to rise further with blood infusion Determination of cardiac output taken after an average of 178 ml of blood had been infused during an 11-minute period showed a calculated decrease in cardiac work

Hemodynamic measurements in the dogs with peripheral fistulas before blood infusion show changes in direction and magnitude similar to those in dogs with aortacaval fistulas except that the left ventricular end-diastolic pressure may or may not be elevated The cardiac response to infusion in these dogs is related to the resting level of left ventricular end-diastolic pressure When this pressure is considerably elevated the response to infusion is similar to that in the dogs with aortacaval fistulas that is cardiac work remains fixed while end diastolic pressure rises further When this pressure is within the normal range the left ventricle increases its cardiac output and cardiac work further with infusion even though the preinfusion cardiac output and cardiac work values are already quite high

In all three groups most of the increase in cardiac response is in the stroke volume since the heart rates do not change greatly and the systemic blood pressure response is not large They are somewhat in contrast with the mountain and sea level studies of the treadmill subjects in which the heart rate changes are much more evident and effective in determining the level of cardiac output and cardiac work

Values for maximum cardiac work obtained with infusion into the normal dog and into the dog with an artery vein fistula are of the same order of magnitude Maximum cardiac work for the normal dog averages 8 9 kg m /min./m.$^2$ for the dog with an aortacaval fistula 6 9 kg m /min /m $^2$ and for the dog with a peripheral fistula 11 3 kg m /min /m $^2$ These values approximate those in human subjects doing heavy exercise in Lima (12 1 kg m /min /m.$^2$) or moderate exercise in the mountains (12 3 kg m /min./m $^2$) They are considerably less than the value of 26 3 kg m /min /m.$^2$ in mountain natives exercising to exhaustion

These data give a rough idea of the magnitude of the possible response of the left ventricle to the stress of an acute increase in blood volume and venous return by blood infusion in the normal dog and in the dog with a fistula and to the stress of muscular exercise in man with increased venous return with and without chronic hypoxia The one is an unusual situation and occurs naturally but rarely The other is something we are doing most of our waking hours In the first in

stance the maximum cardiac output and cardiac work were effected largely by an increased stroke volume and stroke work since the heart rate and effective systemic blood pressure were not greatly increased, in the latter instance maximum response of cardiac output and cardiac work arose primarily from the large elevation of heart rate Only at the extreme levels of external work in the mountain natives did the stroke volume and stroke work show any considerable increase

*Selkurt.* Did the hematocrit in these dogs with fistulas happen to be about normal or what changes did you observe in hematocrit or nutritional level?

*Gregg* Preoperatively and postoperatively the dogs received horse meat once a day and occasionally ferrous sulfate Postoperatively, the hematocrit generally tended to fall but after a month or two they were in good condition and most but not all had an approximately normal hematocrit However, following infusion with whole blood, the hematocrit rose in most dogs Whatever the initial hematocrit, the final hematocrit was higher following blood infusion

*Green* Was the major method of compensation in the second and third groups increased stroke volume?

*Gregg* Since only a small volume of blood was infused in these groups, an appreciable change in stroke volume might not be expected as compared with the normal dog with a very large infusion However, the presence of the fistula did increase the stroke volume and stroke work over the values in the normal dogs despite the considerable increase in heart rate

*Cournand* You have no data on rest pressure in the dogs, in the second and the third group?

*Gregg* They are in Table XXIV For the dogs with aortacaval fistulas, the average control figure for effective end-diastolic pressure in the left ventricle was 26 mm Hg At the time we took our next pressure reading during infusion, the work response of that ventricle was decreasing so the initial pressure figure was regarded as maximum However, in both groups of dogs with fistulas, as infusion was continued beyond the time of maximum cardiac work response, the end-diastolic pressure continued to rise reaching in some dogs very high values—50 to 60 mm Hg However, this was well beyond the maximum work response of the ventricle and hence the curves of left ventricular end-diastolic pressure and cardiac work are deviating markedly

*Wood* How much trouble did you have in determining cardiac output of dogs with central fistulas by the dye-dilution technic? I should think the systemic circulation would be so fast that you would have difficulty in defining the descending slope (12)

*Gregg* It is true that the point of recirculation appears high on the descending slope and that a small error is thus introduced There is an occasional dog in which we certainly would not accept the calculated cardiac output value However since our cardiac output curves are large approximating 10 cm in height and since there is generally about 2 seconds between the peak of the dye dilution curve and the point of recirculation the down slope is well defined in most cases

MECHANISM OF CONTROL OF
STROKE VOLUME AND STROKE WORK

Let us return now to a consideration of the above figures with the hope of attaining some indication of how ventricular function is achieved Is there any way in which we can obtain some indication as to what determines the maximum response of the heart beyond the resting level? Specifically can we associate the changes in stroke volume and stroke work which occur in the infused dogs and in the exercising humans with any particular activity that we can measure in or near the heart? To explain the mechanism of control of stroke volume and stroke work considerable work has been done concerning parameters related to filling and emptying a ventricular cavity Two of these factors the level of atrial pressure and the end-diastolic pressure in the corresponding ventricle just before isometric ventricular contraction have been used to gauge ventricular function Starling and associates (13) found many years ago that in the heart lung preparation as inflow increased atrial pressure often provided a useful method for estimation of spontaneous or induced impairment of cardiac function and its improvement by drugs Wiggers and Katz (14) using the open-chest dog have stressed the close relationship of ventricular end-diastolic pressure to stroke volume and stroke work of the corresponding ventricle until the heart became overloaded Sarnoff (15) has repeated confirmed and greatly expanded some of the older observations by plotting data of atrial pressure and stroke work as ventricular function curves in open chest dogs exposed to increasing ventricular stress We have also obtained excellent correlation between left ventricular end-diastolic pressure and stroke work in the open-chest dog (10)

*Cournand* That is true of the rat and of the rabbit

*Gregg* Yes However caution must be used in the interpretation of such experiments designed to show that ventricular end-diastolic pressure or atrial pressure can be used as a gauge of ventricular function I refer to a group of experiments in our laboratory in which the relation of effective end-diastolic pressure to stroke volume and stroke work was observed in a preparation somewhat closer to the normal situation

Dogs were provided with carotid loops and cardiopexies and trained to run on a treadmill (6) Before exercise, a needle was inserted (and left in place) in the carotid artery for registration of mean blood pressure and for blood withdrawal for cardiac output determination with the densitometer For dye injection, a small, long plastic tube was inserted into a front leg vein For left ventricular end-diastolic pressure, a short (from 6 to 7 cm ) stiff plastic tube was threaded into the cavity through a needle in the pexy This was left in place For phasic intrapleural pressures, a de Pezzer catheter was inserted into the left intrapleural space near the heart and the values obtained were used to correct the directly measured left ventricular end-diastolic pressure These pressure pick-ups were connected to strain gauges and the pressures were recorded optically After obtaining control records, the tubes and needles were disconnected and left in the dog The dog was then exercised on a treadmill at 5 to 12 miles per hour and for as long as 10 minutes The dog was again placed on the table and hemodynamic measurements were repeated within 30 to 60 seconds and as often as desired thereafter Without doubt the data are a combination of the effects of exercise and excitement

Figure 64 illustrates the data from three such experiments Casual inspection of each shows that there is not a good directional correlation between ventricular end-diastolic pressure and stroke work or stroke volume In the first experiment, stroke work shows a downward trend while the end-diastolic pressure rises, falls, and then plateaus In the second, stroke work falls rapidly while end-diastolic pressure is fairly constant In the third, stroke work rises while end-diastolic pressure decreases

Thus in these two conditions—the state of increased blood volume and increased venous return by low infusion rates and the more natural state of exercise and excitement—end-diastolic pressure in the left ventricle is not a dominant factor or indicator of ventricular function

This emphasizes the need for measurement of parameters other than those mentioned Of particular interest would be measurements *in the normal dog of the diastolic and/or residual volume of a ventricle* This would enable us to construct pressure-volume curves of a ventricle under different conditions of stress and possibly to calculate the varying tensions in the myocardial wall With this information, it is believed that many of our experimental and interpretive inconsistencies would disappear However, at present, I am not aware of any method that will give precise values for these variables in animals or in human beings in a state of exercise or indeed in any condition Possibly Dr Bing, who has been active in this field, might wish to comment

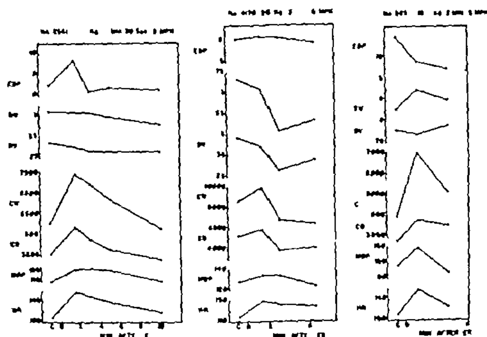


FIGURE 64 Three experiments showing hemodynamic responses in the normal dog before and after exercise EDP is effective ventricular end-diastolic pressure. SW is stroke work in gram meters per beat SV is stroke volume in cubic centimeters per beat CW is cardiac work in gram meters per minute CO is cardiac output in cubic centimeters per minute MBP is mean carotid blood pressure. HR is heart rate C is control Reprinted, by permission from Gregg D E. Sabiston, D C and Theilen E O Performance of the heart changes in left ventricular end diastolic pressure and stroke work during infusion and following exercise *Physiol Rev* 35 132 (1955)

*Bing* The method we tried to devise can only be done if the animal or the patient is at rest and I doubt also whether the method is accurate enough to give values which could be applied to a relationship between diastolic volume and end-diastolic pressure

*Gregg* Developmental approach to the problem has been undertaken in many laboratories and certainly considerable progress has been made Our own unpublished endeavors have included attempts at the construction of area-density curves with scanning technics applied to roentgenograms of a ventricle some time after the injection of small amounts of radio-opaque material to outline the ventricular cavity In addition, we have attempted to measure diastolic volume by following density or conductivity changes in a ventricular cavity following injection of dye or a hypertonic sodium chloride solution into the cavity Thus far these attempts have all been plagued with technical difficulties which have prevented the recording of values acceptable to us

*Cournand:* You have not tried to use Rushmer's technic, with the little clips?

*Gregg* No, we have not done so, however, Dr Rushmer's use of intraventricular gauges for measuring diastolic volume appears to be a very fine technic (16, 17) One of the problems in the use of this method, though, is the difficulty in being sure that the change in the area being measured, that is, the cross sectional area at the level of the gauge, represents directionally a change in volume of the whole ventricular cavity If this should prove to be true, the method should still be used with caution since there remains the problem of assigning quantitative values to ventricular volume I might add that Dr Rushmer, in using these gauges in the exercising dog, has found that the systolic volume of the heart decreases while the diastolic volume is relatively stable, indicating that the increased stroke volume is obtained by squeezing out the residual blood

*Cournand* If I understood you, in dogs the correlation between the increase in effective pressure and the increase in work is fairly good in infusion experiments, but the relationship is not as good in the exercise experiments Of course, the situation with regard to the emptying of the ventricle is possibly not the same In other words, during exercise the peripheral resistance might change very strikingly whereas in infusion the change in resistance might not be so great

*Gregg* Yes, I am sure there is a big difference For example, in the dog, the venous return is greatly increased with these massive infusions so that it would seem necessary for the ventricles to increase greatly their diastolic size and stroke volume, whereas in the exercising man in which the increased venous return arises from a more rapid circulation and increased heart rate there would not seem to be as much necessity for increase in diastolic volume and stroke volume

*Moe·* It seems to me the reflex control of the heart would be entirely different in these two situations

*Gregg* I am sure it is The situation of greater interest is perhaps that of the exercise, since we are performing some form of muscular action during most of our waking hours We do not expose ourselves to blood infusions very often

*Cournand* In one case, you are almost duplicating what Starling was doing, in the other case there is another situation

*Gregg* Yes For example, Dr Sarnoff's ventricular function curves are excellent examples of the close relationship of stroke work to atrial pressure in the presence of acute ventricular loading with increased blood volume, but I rather doubt the data can be transferred to a normal situation where many other variables are changing simultaneously

When in addition to the increased venous return set up by exercise one considers the rapid changes in heart rate, blood pressure regional peripheral resistance, arteriovenous oxygen difference, the waxing and waning of cardiovascular reflexes and the injection of some of Dr Barcroft's epinephrine into the cardiovascular system the situation becomes complex It is quite possible that each of these and additional variables, if applied separately might result in a close correlation between ventricular end-diastolic pressure and stroke work since such a relationship has been found to exist when the ventricle is stressed by infusion in the presence of coronary artery constriction epinephrine infusion etc (15) However it would not be expected that the heart would respond to all these variables as if only one existed or that the level of ventricular function could be gauged by following only ventricular end diastolic pressure or atrial pressure

This raises the question of the value in the normal state of such measurements or correlations with the stress of exercise since each deviation from the correlation of pressure and stroke work would be regarded as a point on a new ventricular function curve It does not improve my thinking or concept of the subject to regard each point as the genesis of a separate function curve

*Merriman* What is the explanation for changing from curve to curve if that is true?

*Gregg* I do not know the real explanation I suppose it is related to the establishment of a new tension in the ventricular wall for a given ventricular diastolic size and hence a different pressure volume curve is established giving a new relationship between ventricular end diastolic pressure and stroke volume or stroke work

*Wood* Is it more likely that it is due to change in nervous activity and to humoral mechanisms?

*Gregg* You mean the effect in muscle?

*Wood* Yes an effect on the muscle fibers due to changes in their chemical (humoral) environment which changes them from curve to curve as was predicted originally by Starling (18) and his colleagues

*Gregg* I cannot answer this because there are no pressure volume measurements where nervous activity and the humoral mechanisms are spontaneously varying

*Bing* It has been shown that the individual heart muscle fiber can also jump from one curve to another as a result of the effect of drugs such as digitalis so what is applicable to the isolated strip may be perfectly well applicable to the whole heart

*Gregg* What you say can well be true but what Dr Wood is speaking of is also quite true Presumably nervous activity humoral mech

anisms, drugs, and other variables operate to change the pressure-volume relationship of muscle by affecting the biochemical status of the heart.

*Wilkins:* If I may go back for a moment to your dogs with arteriovenous fistulas, do you have observations on what happens when a fistula is first opened, then closed, as opposed to when it was *in situ* for a long time and then closed. It is implied in what you showed that you have a different ventricle (in terms that we have been discussing in the last few minutes) after a stress has been sustained and accommodated for, or at least adapted to, as best the animals can for some weeks. After this period they go into a state of "failure" as contrasted with the situation when an arteriovenous fistula is first opened. Do you have data of that kind?

*Gregg:* Yes, we have a fair amount of such data which Dr. Sabiston of our laboratory has accumulated in unanesthetized dogs with an aortacaval fistula. The cardiovascular system of these dogs is certainly under a tremendous strain in the early postoperative period, but aside from increased heart rate, cardiac work, and cardiac output, it does not show too much evidence of this stress. For example, despite the large increase in stroke volume and stroke work occurring as soon as the fistula is opened, the rise in left ventricular end-diastolic pressure lags behind and may not show a significant elevation. However, later on after a number of days or weeks the end-diastolic pressure will rise and this is often coincident with the onset of many of the signs and symptoms of congestive heart failure such as ascites, edema of extremities, and pulmonary edema. In addition, they have reached the end point of maximum cardiac work response. However, I am a little reluctant to type them as in congestive heart failure since they do not respond hemodynamically to digitalis preparations.

## MECHANICAL EFFECTS OF VENTRICULAR SYSTOLE ON CORONARY FLOW

I should like to take up two problems of the coronary circulation that have troubled me for many years. The first problem is the quantitative separation of the mechanical effects on coronary flow of ventricular systole from the influence of the vasomotor state of the coronary vessels. With the methods now available, measurement of change in coronary flow with increased stress is not difficult. For example, with sustained aortic constriction, left coronary inflow measured with a rotameter increased from 55 to 125 ml./min. before any significant change in aortic or central coronary pressure occurred (Figure 65). It is obvious from the decreasing ratio of pressure to flow that the coronary bed was gross-

ly dilated However this determination alone does not reveal how the heart was able to obtain an extra influx of blood just before its work increased

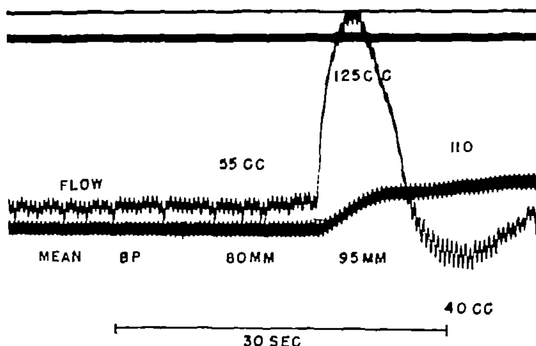



FIGURE 65 Reproduction of record showing the effect of mechanical constriction of the thoracic aorta on left coronary inflow as measured with the rotameter Constriction was maintained throughout the record

*Moe* How was the aortic pressure raised?

*Gregg* By mechanical constriction of the aorta with an adjustable clamp This flow response does not always obtain but it is not too difficult to elicit

*Remington* Where was this clamp?

*Gregg* On the aorta, in the thoracic region. Of primary interest is the means by which the heart can dilate its coronary bed and increase its coronary flow and oxygen supply The mechanisms involved in the heart are those which cause coronary dilation by relaxation of the intrinsic smooth muscle of the coronary vessels and those which do not act directly on smooth muscle but indirectly or passively alter the coronary flow through the mechanical effects of ventricular systole

Let us first consider those passive *mechanisms regulating coronary* flow The importance of the problem lies in the strong possibility that much of the control of coronary flow lies in these extravascular supporting *mechanisms* in the myocardium We have to make up our minds as to how myocardial activity controls the coronary flow that is

whether it serves as a peripheral resistance to reduce flow or whether it augments coronary flow by massaging blood through its walls The direction of the effect and its magnitude must be known Its importance is indicated by a number of studies *a*) following acute occlusion of a major ramus of a coronary artery the coronary pressure beyond the point of occlusion is sizeable during systole and undergoes cyclic variations with each heart beat (19), *b*) when a left coronary artery branch is perfused at different pressure levels, systolic inflow is cut off at a level of perfusion pressure approximating the aortic systolic pressure (20), *c*) Figure 66 shows a phasic flow curve taken with an orifice meter from a branch of the left coronary artery in which the normal central pulsatile coronary pressure and peripheral factors affecting flow are all operating simultaneously It is observed that the systolic rate of inflow is less than the diastolic rate (19, 21) Hence, change in the relative length of time occupied by systole and diastole can affect mechanically mean coronary inflow For example, a decrease in the systole/cycle ratio would increase coronary inflow These experiments suggest that left ventricular activity acts to reduce coronary flow

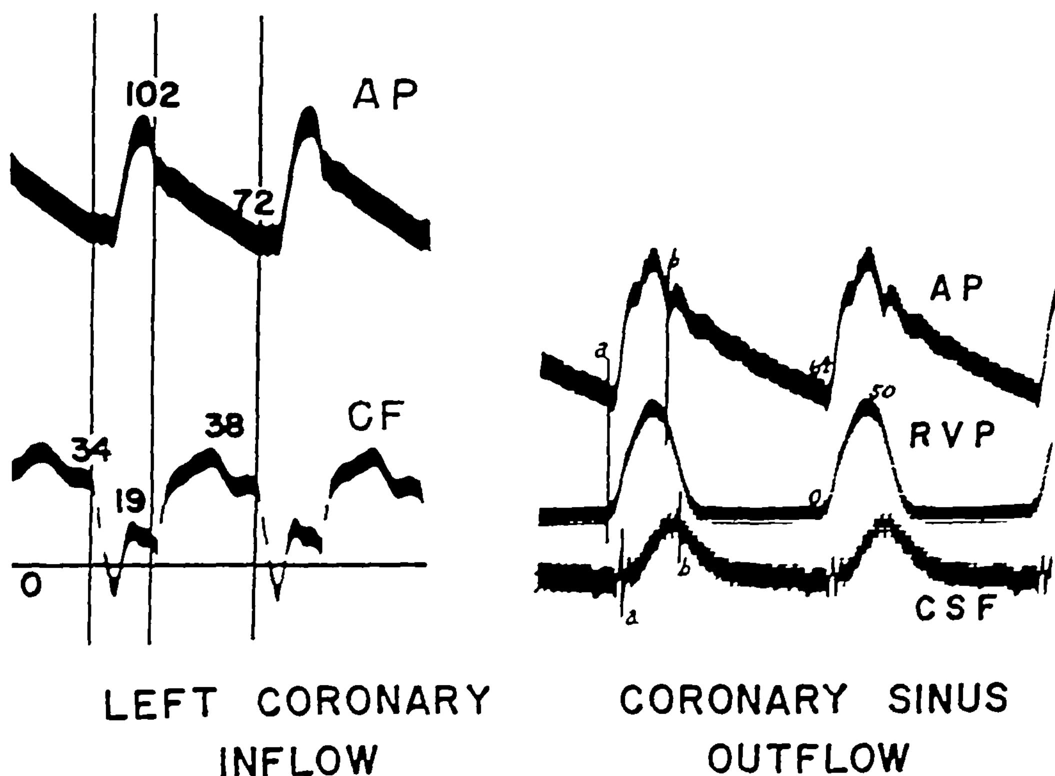



FIGURE 66 Reproductions of original records showing phasic inflow in coronary sinus and circumflex ramus of left coronary artery in open-chest dog AP is aortic pressure RVP is right ventricular pressure CF is coronary inflow with orifice meter CSF is coronary sinus flow with Pitot tube meter

*Bing* Is this phenomenon an example of intramural resistance?

*Gregg* I think so being activated at that time A final bit of evidence is contained in Figure 66 showing phasic flow changes recorded with a Pitot tube in the coronary sinus of the anesthetized open-chest dog During systole coronary sinus flow is increased while during diastole flow is greatly reduced suggesting that ventricular systole acts to augment coronary flow (22 23) This contrasts with the picture in the left coronary artery in which myocardial action has the reverse cyclic effect on inflow In terms of the action of the myocardium the problem is Which of these effects on flow is the greater in magnitude that is is the mean flow through the coronary vessels increased or decreased by myocardial activity? No final answer can be obtained from consideration of these coronary inflow and outflow curves since it is not known whether the changing flow rates in the superficial coronary arteries and coronary veins (where the phasic flows were recorded) represent flow through the myocardial wall of the left ventricle

As a means of solving this problem, we have adopted the procedure of stopping ventricular activity for a sufficient period until a new coronary flow equilibrium is established and then ascertaining whether coronary inflow and coronary sinus outflow rise or fall The preparation consists essentially of the open-chest dog in which the coronary arteries or a major branch of left coronary artery is perfused under a constant pressure approximating the prevailing mean aortic pressure The inflow in a coronary artery (and often the coronary sinus outflow) is quantitated with a recording rotameter (24) together with the mean coronary perfusion pressure mean aortic pressure and at times left ventricular end-diastolic pressure For the coronary sinus flow blood is led through a recording rotameter connected on one side to a polyvinyl tube tied into the coronary sinus and on the other side joined to a plastic tube opening into the right atrium or to the atmosphere Continuous pressure and flow measurements are made while the heart is normally beating and then during ventricular asystole induced generally by vagal stimulation In many experiments changes in coronary inflow and coronary sinus outflow were followed in the same experimental setup when ventricular activity was reduced by ventricular fibrillation induced by electrical means

Induction of ventricular fibrillation invariably increases coronary inflow and coronary sinus outflow by a variable amount A typical effect is shown in Figure 67 in which flow into the common left coronary artery was measured simultaneously with coronary sinus flow At a constant perfusion pressure of 85 mm Hg approximating mean aortic pressure, left coronary inflow rose within 1 second after fibrillation from

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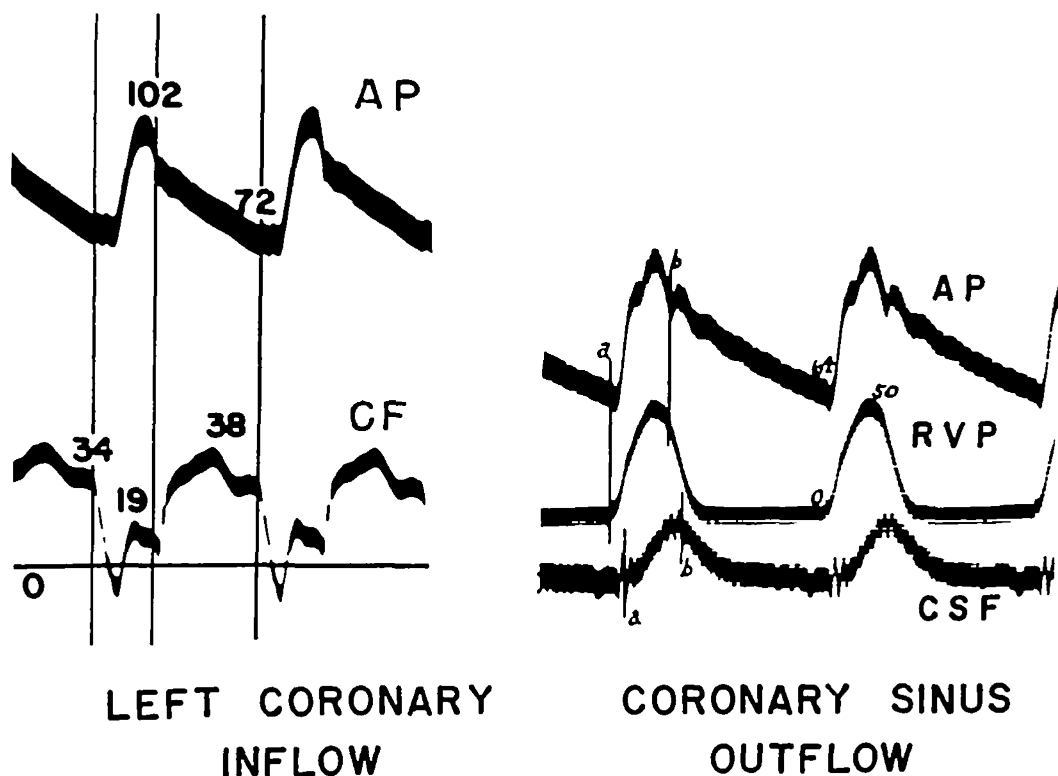



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a control value of 119 ml /min in the beating heart to 140 ml /min in the fibrillating heart At the same time, coronary sinus flow starting at 74 ml /min decreased momentarily with fibrillation and then quickly rose above control level in 2 seconds and reached 121 ml /min within 12 seconds There was a very slow decline in both curves during the next 2 minutes (record not shown) These large increases in coronary inflow and coronary sinus outflow must represent a large decrease in peripheral resistance occasioned by the absence of systole but how nearly the existing state of fibrillation represents an asystolic state is not known

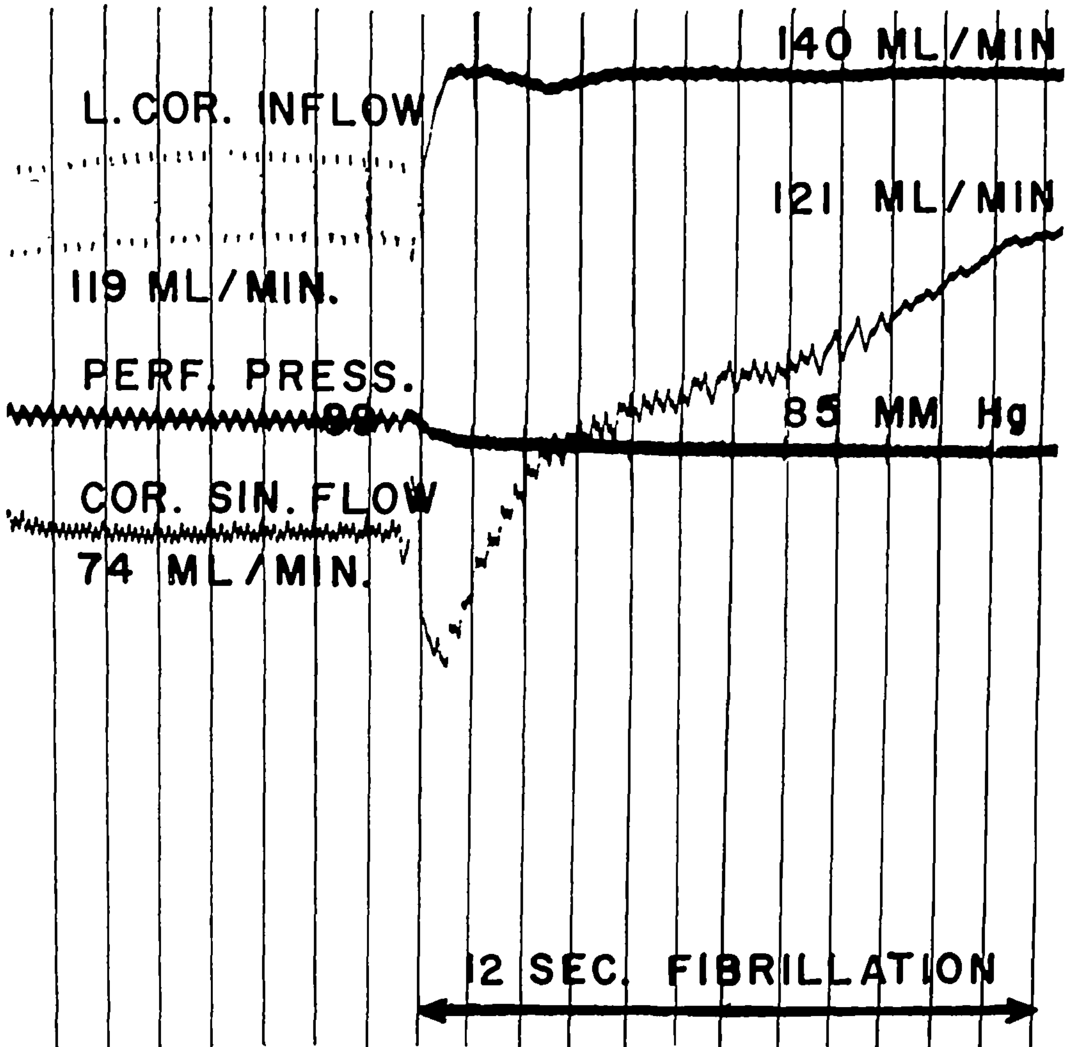



FIGURE 67 Reproduction of original record showing augmentation in left coronary inflow and coronary sinus outflow during ventricular fibrillation

*Cournand* What happened to the blood pressure?

*Gregg* The aortic blood pressure decreased It was not recorded in

this record An estimate would be that it might drop 5 to 10 mm Hg in the first second Some of the later figures may show a record of this decline

*Moe* There was no blood flowing into the right coronary artery at this time?

*Gregg* Not in this dog However in many dogs both coronary arteries were perfused simultaneously

*Cournand* How long did the pressure persist in the right coronary artery?

*Gregg* It might possibly drop 10 mm Hg in the first 1 to 2 seconds of asystole and it would continue to decline Consequently right coronary inflow was dropping rapidly during asystole There is little doubt that in the dog whose coronary flow is shown in Figure 67 a very small volume of the blood that entered the left coronary artery was draining by collaterals into the right coronary artery bed and thus accounting for a small portion of the augmentation of left coronary inflow during asystole

*Barcroft* Is there not a close analogy between the behavior of the coronary flow here and that in the skeletal muscle? Kramer and his colleagues (25) measured the blood flow in the isolated gastrocnemius muscle before during and after a period of rhythmic contraction (Figure 68) This is the period of rhythmic exercise They found that the blood flow rose moderately during the exercise but that immediately after the exercise stopped the flow increased much further and then fell away more or less in an exponential manner to the original resting rate Their explanation was that the vessels were being dilated by a local process but this vasodilation was opposed by mechanical hindrance to the flow As soon as the exercise stopped the mechanical hindrance was removed and the true effect of the vasodilation was evident Later this gradually subsided

*Gregg* Yes the pattern of response of coronary flow with ventricular fibrillation is similar to that observed by Kramer following cessation of rhythmical contraction of skeletal muscle However the augmentation of flow in the left coronary artery and in the coronary sinus has been maintained generally for at least 1 to 2 minutes

*Stead* Is there any information on the rate of inflow in an empty heart as contrasted with one that has the usual amount of residual blood?

*Gregg* Yes inflow is more rapid in the heart with empty vessels but this does not explain the portion of the coronary inflow and outflow curves in which we are interested I would estimate the capacity of the left coronary bed in a good sized dog to be no more than 1 to 3 ml and

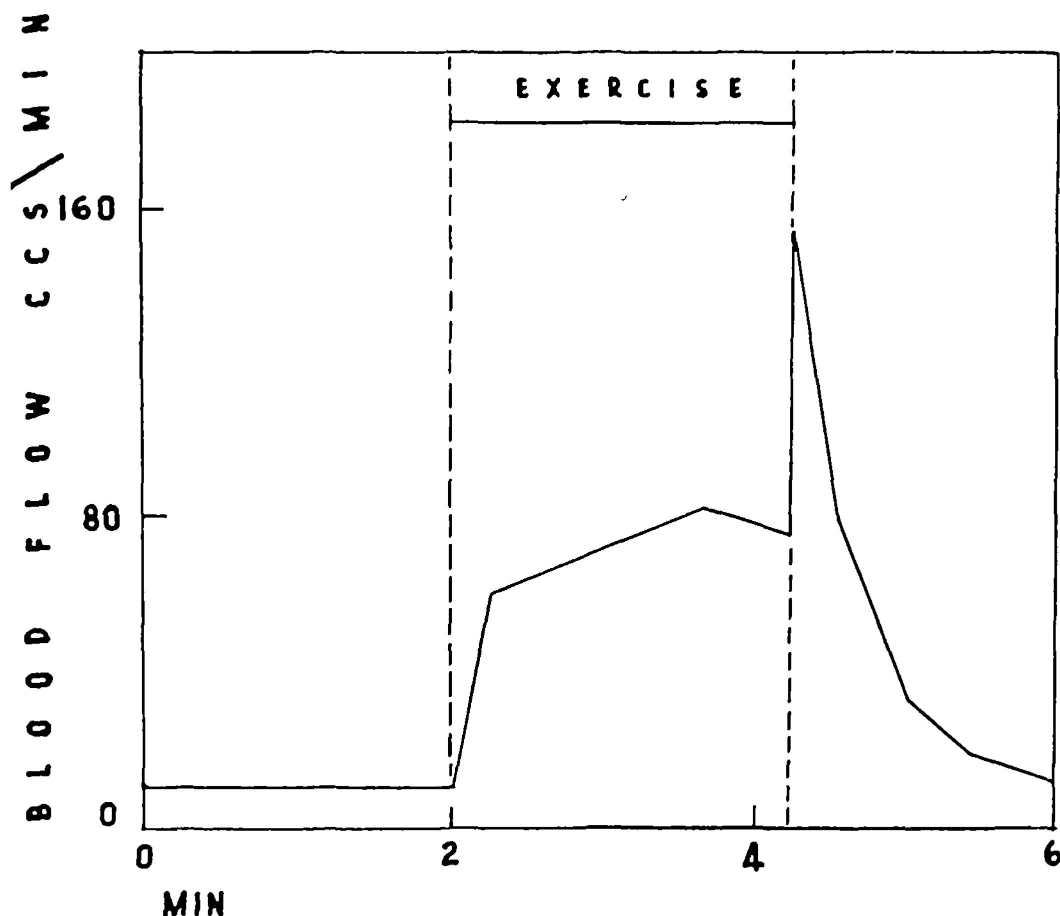



FIGURE 68 Experiment showing the effect of rhythmic exercise on the blood flow through the chloralosed dog's gastrocnemius muscle Immediately after exercise mechanical hindrance to the passage of blood through the muscle ceases and the flow increases abruptly As recovery occurs the blood flow returns exponentially to the resting rate Reprinted, by permission, from Barcroft, H, and Swan, H J C *Sympathetic Control of Human Blood Vessels* London, Edward Arnold & Co, 1953

thus filling of the bed would soon be over whereas the large increase in coronary inflow (and outflow) is maintained for a relatively long time

*Stead* I was thinking in terms of Dr Barcroft's question, whether what you lost by systole you might also gain somewhat by diastole, so to speak, so that the two might tend to balance each other somewhat

*Barcroft* Yes, in the skeletal muscle it appears that you put a series of checks on the flow

*Montgomery* This is a single muscle contraction you are speaking of?

*Barcroft* Yes

*Montgomery* And Dr Gregg was speaking a while ago of a single

muscle contraction Isn t this quite analogous to the flow changes at each contraction?

*Gregg* If a left ventricle is placed in a fibrillatory state and the intraventricular pressure decreases greatly and averages about 10 mm Hg for a cardiac cycle then without much doubt the resistance to coronary flow within the myocardial wall must be considerably reduced The resultant increase in coronary inflow and outflow is believed to be caused by the removal of the active co-ordinated contractile process

*Bing* You mean you remove the intramural resistance?

*Gregg* I don t know how much we remove it in the fibrillating heart

*Bing* It certainly cannot be much

*Gregg* It is I believe quite a bit lower than in the beating heart since as we will see a little later coronary flow increments of the same order of magnitude are observed during ventricular asystole by vagal stimulation

*M Knisely* Some years ago members of my laboratory focused microscopes on the superficial layers of the myocardium of the beating hearts of frogs to see whether the contracting muscle fibers expanded enough to squeeze the blood capillaries between them sufficiently to stop the blood flow in the capillaries The particular procedure which made many sharp clear observations possible consisted of focusing the microscope at a given position of the heart beat cycle at which the heart stood still for a moment By pressing slightly against one or more parts of the animal s body it was possible to have this moment of physical arrest occur during several different portions of the cardiac cycle Thus the conditions of the vessels and blood in the myocardium were observed in sharp focus many times at each of the successive phases of the cardiac cycle, but no microscope field was held in focus during a single complete cardiac cycle The observations under the conditions of these experiments were that the blood flow was stopped in the capillaries of the frog myocardium during each and every systolic phase of the cardiac contraction The blood flowed in torrents through these vessels during the diastolic portions of the cycle It seems probable that very high speed motion pictures taken through the miscroscope would make it possible to record portions of such cycles and to measure the diameters of the vessels

*Gregg* The same trend in coronary inflow (and coronary sinus flow) was obtained by the induction of periods of asystole by vagal stimulation In the experiment reproduced in Figure 69 inflow in the circumflex branch of the left coronary artery maintained under a constant pressure of 78 mm Hg (somewhat less than the prevailing aortic pressure of 92 mm Hg) rose from 35 to 50 ml /min during a short period of

asystole induced by vagal stimulation During the asystolic period, the left ventricular end-diastolic pressure remained at 6 5 mm Hg I believe Dr Moe would criticize the significance of this flow response on the ground that both coronary arteries should have been perfused during asystole or during fibrillation to prevent blood from passing from the perfused artery into the nonperfused artery As I have already indicated, we do have many observations with the left and/or right coronary artery being perfused simultaneously with similar directional flow changes The record of mean aortic pressure gives values to answer Dr Cournand's earlier question The rate of pressure fall was about 10 mm Hg per second

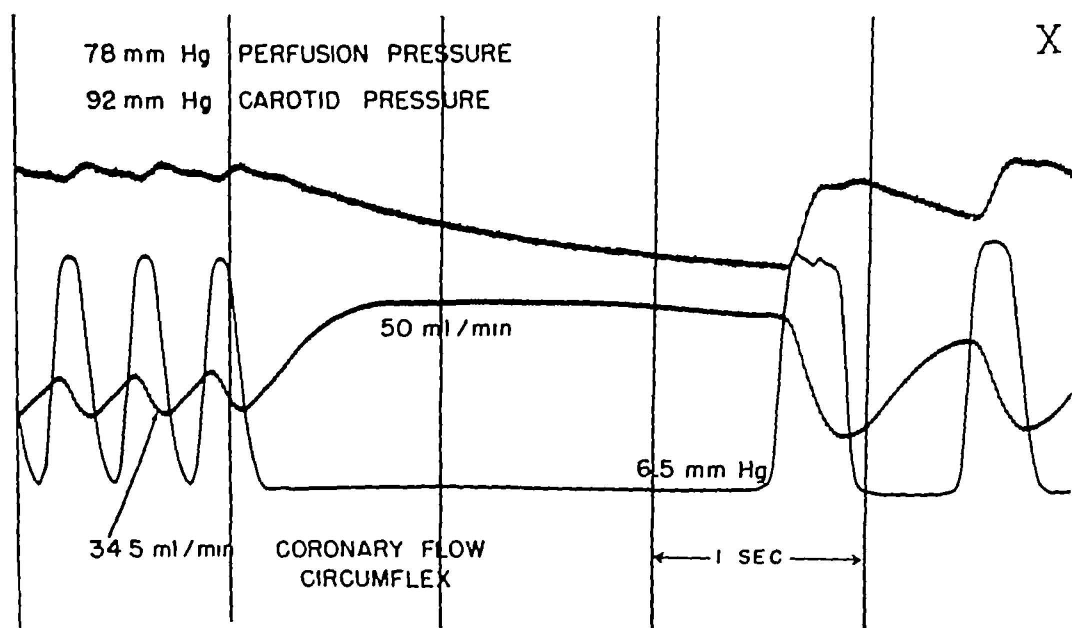



FIGURE 69 Reproduction of original record showing the effect of asystole on blood flow in left circumflex ramus Upper curve, mean carotid blood pressure, middle curve, coronary flow, bottom curve, left ventricular pressure

*Moe* This record was taken during vagal stimulation?

*Gregg* Yes We have had much difficulty in maintaining the ventricles of such hearts in the relaxed state for any long period of time with vagal stimulation or with other procedures The question can be raised whether a portion of the coronary flow increase during vagal stimulation is explainable on some basis other than the removal of myocardial contraction I rather doubt it, because of the initial rapidity of the rise of coronary inflow and its maintenance at this level and because following induced ventricular fibrillation the addition of vagal stimulation has been found not to increase further coronary flow

Table XXV gives data showing the direction and magnitude of

changes in left coronary inflow and coronary sinus outflow during electrically induced ventricular fibrillation and during ventricular asystole caused by vagal stimulation This data was obtained with either the common left coronary artery or both coronary arteries perfused at a constant pressure The responses were induced with a variable relation of aortic to constant perfusion pressure (Perfus Press ) with varying degrees of blood oxygen saturation and in the presence of drugs The table indicates that augmentations of coronary inflow with both fibrillation and asystole were in the same general range the flow increases exceeded the control values in the beating heart by 25 to 81 per cent As a result pressure flow relationship decreased the magnitude of the decrease was from 24 to 25 per cent

*Moe* Perfusing all the coronary branches doesn t change the fundamental conclusion?

## TABLE XXV

### Effect of Ventricular Fibrillation and Asystole on Left Coronary Inflow

| Perfus Press mm Hg | Left Coronary Flow | | | Pressure/Flow | | | |
|---|---|---|---|---|---|---|---|
| | Cont * ml | Exper † ml | Inc % | Cont ml | Exper ml | Change ml | Dec % |
| | | | *Fibrillation* | | | | |
| 100 | 32 | 43 | 33 | 3.1 | 2.4 | 0.7 | 25 |
| 74 | 23 | 41 | 76 | 3.2 | 1.8 | 1.4 | 43 |
| 80 | 40 | 67 | 70 | 2.0 | 1.2 | 0.8 | 41 |
| 34 | 33 | 53 | 58 | 1.0 | 0.6 | 0.4 | 37 |
| 76 | 59 | 74 | 25 | 1.2 | 1.0 | 0.2 | 24 |
| | | | *Asystole* | | | | |
| 78 | 51 | 93 | 81 | 1.5 | 0.8 | 0.7 | 45 |
| 80 | 41 | 61 | 51 | 2.0 | 1.3 | 0.7 | 34 |
| 91 | 147 | 180 | 23 | 0.6 | 0.5 | 0.1 | 17 |
| 89 | 93 | 154 | 66 | 1.0 | 0.6 | 0.4 | 40 |
| 96 | 109 | 138 | 26 | 0.9 | 0.7 | 0.2 | 22 |

*Control data.
†Experimental data.

*Gregg* No It will, however, change the magnitude of the effect by a very small amount since a small volume of blood passes from one coronary artery to the other (or to a coronary arterial branch) unless the perfusion pressures in both arteries are approximately the same

In summary then, when co-ordinated shortening of left ventricular muscle fibers is removed, both left coronary artery inflow and coronary sinus outflow rise considerably The new flow level is believed to represent that state of dilation of the left coronary artery attributable to the intrinsic smooth muscle in the walls of the coronary vessels The extent of augmentation of coronary inflow with these procedures is believed to represent quantitatively the magnitude of the limitation of coronary inflow exerted by the extravascular or mechanical factors in the ventricle Myocardial action during systole tends to throttle coronary flow through the left ventricular wall This factor is variable and large, and can reduce the left coronary inflow by as much as 50 per cent The asystolic technic is believed to provide a method of separating and quantitating those mechanical factors governing coronary flow and those factors having a direct action on the smooth muscle of the coronary bed

*Green* Would you conclude from this that the fibrillation process itself exerts a mechanical impediment?

*Gregg* No, or at least probably no more than the asystolic process because if a heart is successively fibrillated, countershocked, and then placed in asystole with vagal stimulation, and at the same time the common left coronary artery inflow is measured in the presence of a constant perfusion pressure, it is found that peak flow values during the fibrillation and asystolic periods are about the same Of course, placing the hearts in asystole is a much more convenient procedure

*Green* Have you taken a heart, put it in asystole, and then subsequently fibrillated that same heart to see what effect that onset of fibrillation had on the flow?

*Gregg* No This has not been done

METABOLISM OF THE HEART DURING DIASTOLE

The second problem I wish to consider is the measurement of the metabolism of the heart during diastole Knowledge of the economy with which the myocardium utilizes oxygen depends upon its solution An approximation to the efficiency of the whole body during exercise can be obtained by measuring the external body work and dividing this by the difference between total body oxygen consumption and the oxygen usage of the body during rest Similarly, the efficiency of a beating heart can be calculated from the relation of cardiac work to the difference between the oxygen usage of the beating heart and the oxygen con-

sumption of the resting heart However the oxygen consumption during the relaxed or resting phase of the cardiac cycle is not measurable and hence is of unknown magnitude Its inclusion in the efficiency calculation gives too low an efficiency at low levels of cardiac work while at high levels of cardiac work its presence gives the illusion of a rising efficiency

It occurred to us that the asystolic heart supplied the physiological situation in which the resting metabolism of the heart could be measured and would thus permit the determination of a more nearly precise value for cardiac efficiency Accordingly left coronary inflow and the coronary arteriovenous oxygen difference were measured continuously as the exposed dog heart was put into asystole by vagal stimulation The experimental procedures were similar to those already described with the addition that for the determination of its oxygen saturation coronary sinus blood was sampled either continuously or intermittently by pulling it by syringe through a densitometer (2) the other end being connected

TABLE XXVI

Effect of Ventricular Asystole and Fibrillation on the Oxygen Consumption of the Left Ventricle

| State | M B P mm Hg | Left Coronary Flow | | Coronary Sinus Flow | | C.S A V $O_2$ Dif | $O_2$ Usage ml/min |
|---|---|---|---|---|---|---|---|
| | | ml/min | % Dif | ml/min | % Dif | | |
| Cont | 120 | 105 | ---- | 54 | ---- | 11 5 | 12 1 |
| Asyst. | | 168 | +60 | 41 | −14 | 6 1 | 10 2 |
| Cont. | 117 | 95 | ---- | 34 | ---- | 10.8 | 10 2 |
| Asyst | | 142 | +50 | 48 | +40 | 7 4 | 10 5 |
| Cont | 115 | 95 | ---- | 34 | ---- | 11 9 | 11 3 |
| Asyst | | 134 | +41 | -- | ---- | 5 2 | 7 0 |
| Cont | 118 | 94 | ---- | 38 | ---- | 5 8 | 5 4 |
| Asyst | | 166 | +76 | 59 | +56 | 3 3 | 5 4 |
| Cont | 108 | 125 | ---- | -- | ---- | 14 5 | 18 1 |
| Asyst. | | 147 | +18 | -- | ---- | 10 2 | 15 0 |
| Cont. | 85 | 60 | ---- | -- | ---- | 13.2 | 7 5 |
| Fib 2 | | 40 | −33 | -- | ---- | 11 5 | 4 0 |

to a small plastic tube threaded down the larger tube to a position just within the coronary sinus

Table XXVI illustrates some of the preliminary data These show that oxygen consumption of the myocardium during prolonged asystole (up to 30 seconds) may be only moderately reduced from that obtained just before asystole in the naturally beating heart The usual changes during asystole are a rise in left coronary inflow and a marked decrease in coronary sinus arteriovenous oxygen difference combining to give a reduced figure for oxygen usage as compared with that during the control period in the beating heart The changes beyond 30 seconds of asystole are not known

When co-ordinated contractions are removed by induced ventricular fibrillation, oxygen usage is also fairly well maintained initially, but after a longer period of fibrillation this value is considerably reduced In the example in Table XXVI, at the end of 2 minutes, it is reduced from 7 5 ml to 4 0 ml /min This confirms earlier work (26)

*Montgomery* How long were the asystoles after the termination of the last contractions?

*Gregg* We have not been able to extend this period beyond 30 seconds It is difficult to believe that these figures represent the resting metabolism of the heart However, we are confident that the values are essentially correct and represent the amount of oxygen retained by the left ventricle during these periods of ventricular asystole or fibrillation

*Bing* These are all perfused coronary arteries?

*Gregg:* That is correct

*Stead* This would lead one to think of the heart as normally having an oxygen debt

*Gregg* It certainly would As I indicated earlier, it was hoped that these values could be used to calculate ventricular efficiency That, of course, would be hazardous Possibly Dr Bing can help us with their interpretation

*Bing.* I do not know what they mean If this is true—and it certainly seems to be—the efficiency which we usually calculate for the left ventricle in the human heart would be far too low

In other words, if the oxygen uptake or the oxygen usage of the heart is to a large extent due to the resting metabolism, then the oxygen used for useful work would be much too high in our calculations and the efficiency of the heart would be much greater Simply stated, the efficiency of conversion of chemical energy to useful work would be a great deal higher

Of course, what you measure here in these oxidative figures may be simply the efficiency of energy production in the muscle, the figures for

the efficiency of energy production in the citric acid cycle are close to 60 per cent It doesn t really surprise me to find such relatively high oxygen figures in your results What you measure, Dr Gregg is the metabolism of the heart at rest but the term fibrillation implies of course that there is some activity We found that the first metabolic changes that happen during fibrillation that is as soon as a sample can be taken are indicative of a very severe anoxia of the heart muscle Pyruvate lactate and inorganic phosphorus appear in vein blood in increased amounts It would be very important to check up on some of the metabolic pat terns in the dogs in which the coronary artery is perfused in order to determine whether or not energy production has been impaired Have you made any metabolic studies?

*Gregg* No

*Montgomery* I wondered if you had related this to the oxygen uptake per gram of muscle with barbiturates and then gone back to simple oxy gen uptake to see what might be expected to be the basic oxygen uptake

*Gregg* No

*Montgomery* There are figures for that are there not?

*Gregg* Yes we have made measurements of *in vitro* oxygen consumption in myocardial slices before and during ventricular fibrillation when the left coronary artery inflow was maintained and was not maintained In the presence of ventricular fibrillation without maintenance of cor onary perfusion, oxygen consumption in biopsied left ventricular tissue is significantly elevated In ventricular fibrillation with coronary perfu sion there was no significant change in the *in vitro* oxygen consumption from that in the beating heart (26)

*Montgomery* In other words the 4-ml value (Table 26) is about like a barbiturate figure for oxygen usage in a nonbeating isolated heart

*Barcroft* Might I refer once more to the work by Kramer and his col leagues (27) I think I am right in saying that they also followed the oxygen consumption changes of the muscle before during and after periods of rhythmic contraction Probably Dr Gregg is more familiar than I am with this particular work

*Gregg* I am sure Prof Barcroft is correct

*Barcroft* I think they did and my recollection is that they found that the oxygen consumption increased during the contraction period and that the oxygen consumption fell off exponentially afterward as Dr Stead stated

If there is an analogy between the behavior of the heart and the be havior of the skeletal muscle that might lead one to suppose that about 15 seconds after the end of the contraction of the heart would perhaps correspond with a point somewhere on the decline of the oxygen usage

in the skeletal muscle If this process were falling off more or less exponentially in the heart as it does in skeletal muscle, then perhaps that might explain to some extent why the figure with the fibrillating heart is lower The interval was longer with the fibrillating heart, although the fibrillating heart is not quite analogous with an asystolic heart because the asystolic heart would probably be more at rest than the fibrillating heart which is twitching all the time

*Bing* I do not think, Dr Stead, that you can use this as evidence of oxygen debt Dr Gregg supplies oxygen to the heart at all times, as I understand it, you would have to demonstrate an accumulation of metabolites which are burned during the recovery phase, I do not see how you can make a conclusion without this evidence

*Barcroft* I think Dr Kramer did use the term "oxygen debt" for the intake of oxygen after the end of contraction

*Shorr* We have some figures for the oxygen debt of mammalian skeletal muscle strips following a one-second tetanus at 37 5° C It takes about 30 seconds for the heat production to return to resting values and hence for the oxygen debt to be paid (28)

*Wood.* Dr Gregg, have you done any serial arteriovenous differences during periods of asystole? I would think if it were along the same lines as Dr Barcroft's reasoning, a decline would occur, if you took a continuous sample through your densitometer, you should see it

*Gregg*· I have no doubt that we will find what Dr Barcroft has indicated During ventricular asystole and after the initial rise of per cent oxygen saturation in the coronary sinus and of coronary inflow, the latter value can be observed to decline somewhat, so that it is quite possible that after a period of ventricular arrest longer than 30 seconds the oxygen usage will reach a lower level

*Green* If an oxygen debt were being paid off, there should be a much greater change in the oxygen utilization between the control and the experimental period

*Bing* That is what I tried to say

*Green* Is there some possibility that there is a different type of coronary sinus drainage between the normal and the asystolic heart so that there is an artifact type of record in one or the other situation so far as the total oxygen situation is concerned?

*Gregg* You mean that we may be withdrawing oxygenated blood from the left ventricle through thebesian-like connections

*Green* I would not care to say what the error was, but have you ruled out the possibility that there is differential draining under different conditions?

*Gregg* There are arteriovenous shunts in the coronary bed and it

could be that some blood is traversing them as the heart relaxes I know of no method to test this possibility critically However the associated rise of coronary sinus flow during asystole and ventricular fibrillation would mitigate this occurrence

*Shorr* You cannot avoid the fact that oxygen is used Regardless of the dissipation it is used It disappears

*Bing* It would disappear Dr Shorr but the energy producing process which is continually going on in this muscle necessitates the use of oxygen.

*Shorr* Yes but then you have to assume these processes are going on at such a rate as to require the same amount of oxygen as when the muscles are working

*Moe* We know that the mean oxygen tension in the whole muscle mass must be considerably less than in the arterial blood and if the heart in asystole used absolutely no oxygen at all if its metabolism were zero how long would it take before the coronary sinus blood would come into equilibrium with the arterial blood? All we know here essentially is that oxygen has been removed from the blood in passing through the heart. We do not know that it has been used

*Shorr* How else do you remove oxygen except by using it? You cannot force the oxygen to be used if the muscle is only working to a much lower extent

*Moe* It will diffuse from blood into tissue as long as the tissue tension is less

*Shorr* At a steady state are you going to keep on losing oxygen continuously?

*Nickerson* Dr Lee (29) has studied oxygen consumption in isolated papillary muscles where long periods of asystole are possible He found that the $Q_{O_2}$ was increased about 50 per cent above the resting rate by 1 per second stimulation of the muscle

*Gregg* The data which I have presented are believed to represent the amount of oxygen retained or used by the heart for the performance of its work after the work period has been terminated by asystole I would feel that this is a metabolic retention and might be called the oxygen debt of the heart

*Stead* Dr Bing can you tell us how the amount of lactic acid which is coming out of the heart at this time compares with that which comes out of the skeletal muscle when it is building up an oxygen debt?

*Bing* I do not know about skeletal muscle The only experiments (30) I have which are relevant to your question are those that have been made on the fibrillating heart without maintaining any perfusion whatsoever and I do not think these data are at all comparable because in

that case you cannot speak of any oxygen debt, as circulation is not re-established and a "debt" cannot be measured

*Stead* Does lactic acid appear in the coronary sinus in the normal beating heart?

*Bing* It does not The normal heart uses up a very considerable amount of lactate

*Stead*· It never makes it, so far as you know, under normal circumstances?

*Bing* No, and not even in moderate ischemia does it produce lactate If you produce experimental coronary occlusion with glass spheres, pyruvate alone appears in coronary vein blood But if myocardial ischemia is severe, then both pyruvate and lactate appear in coronary vein blood with great rapidity and in very sizeable amounts It is just a question of how severe the myocardial anoxia actually is

*Stead* Dr Gregg, did you tell us how close these are to the top figures you can obtain in coronary circulation with these particular kinds of pressure? How much, with administration of drugs or other things, can the coronary flow go above this 168 you have for the left coronary? Do you know where they stand in regard to the state of maximum coronary flow?

*Gregg* I would say that this flow figure would be not more than 50 to 60 per cent of the maximum flow possible for a heart or dog of this size

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